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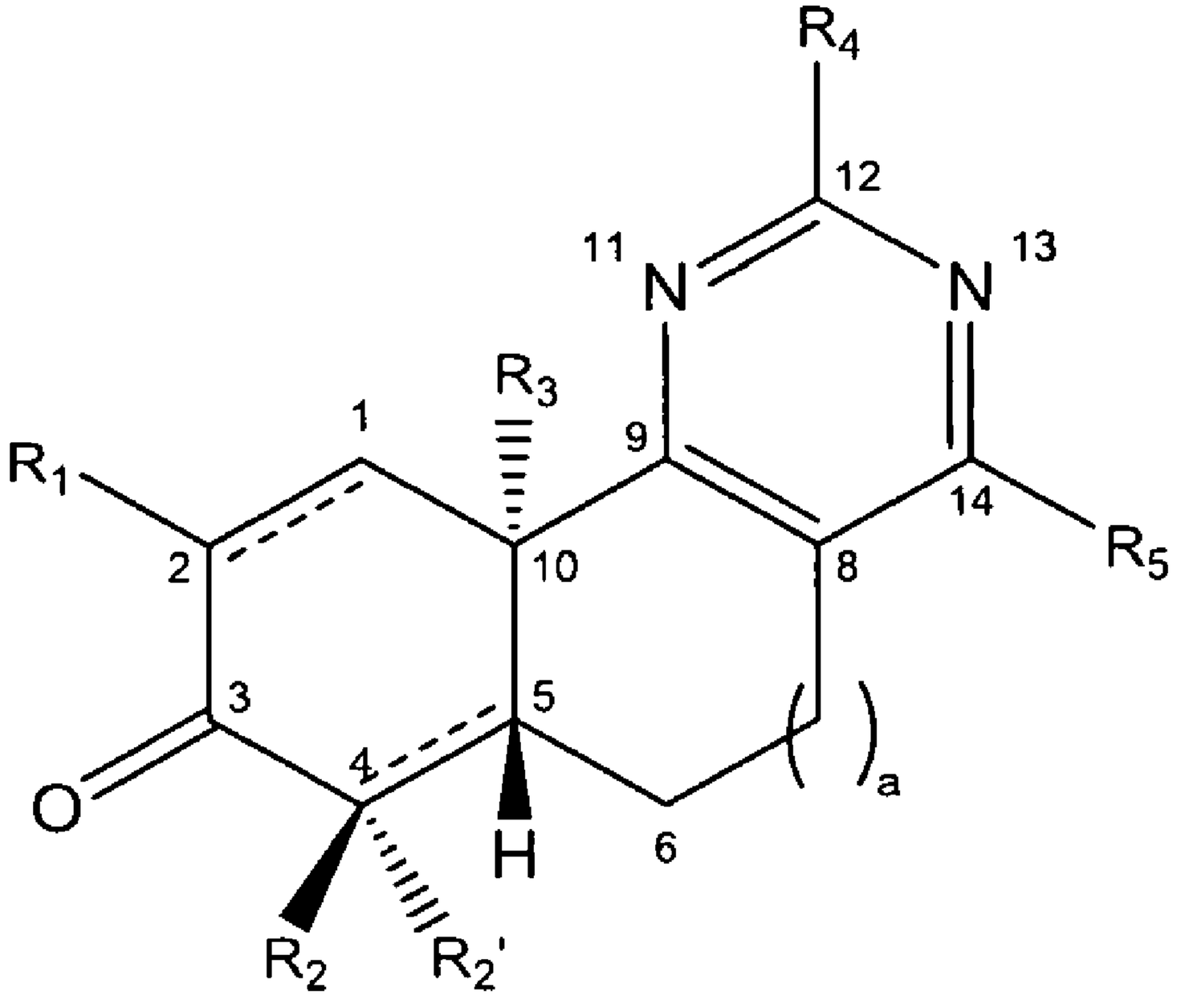
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(71) Demandeur/Applicant:
REATA PHARMACEUTICALS, INC., US

(72) Inventeurs/Inventors:
JIANG, XIN, US;
BENDER, CHRISTOPHER F., US;
VISNICK, MELEAN, US;
HOTEMA, MARTHA R., US;
SHELDON, ZACHARY S., US;

(54) Titre : DERIVES ENONE DE PYRIMIDINE TRICYCLIQUE POUR L'INHIBITION DE RORΓ ET D'AUTRES UTILISATIONS

(54) Title: PYRIMIDINE TRICYCLIC ENONE DERIVATIVES FOR INHIBITION OF RORΓ AND OTHER USES



(57) Abrégé/Abstract:
Disclosed herein are compounds of the formulas: as well as analogs thereof, wherein the variables are defined herein. Also provided are pharmaceutical compositions thereof. In some aspects, the compounds and compositions provided herein may be

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(72) Inventeurs(suite)/Inventors(continued): LEE, CHITASE, US; CAPRATHE, BRADLEY WILLIAM, US; BOLTON, GARY, US; KORNBERG, BRIAN, US...

(74) Agent: BERESKIN & PARR LLP/S.E.N.C.R.L.,S.R.L.

(57) Abrégé(suite)/Abstract(continued):
used to inhibit RORγ and/or reduce the expression of IL-17. Also provided are methods of administering compounds and composition provided herein to a patient in need thereof, for example, for the treatment or prevention of diseases or disorders associated with inflammation or autoimmune disorders.

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(71) Applicant: **REATA PHARMACEUTICALS, INC.** [US/US]; 2801 Gateway Drive, Suite 150, Iriving, TX 75063-2648 (US).

(72) Inventors: **JIANG, Xin**; c/o 2801 Gateway Drive, Suite 150, Irving, TX 75063-2648 (US). **BENDER, Christopher, F.**; c/o 2801 Gateway Drive, Suite 150, Irving, TX 75063-2648 (US). **VISNICK, Melean**; c/o 2801 Gateway Drive, Suite 150, Irving, TX 75063-2648 (US). **HOTEMA, Martha, R.**; c/o 2801 Gateway Drive, Suite 150, Irving, TX 75063-2648 (US). **SHELDON, Zachary, S.**; c/o 2801 Gateway Drive, Suite 150, Irving, TX 75063-2648 (US). **LEE, Chitase**; c/o 3915 Research Park Drive, Suite A-1, Ann Arbor, MI 48108 (US). **CAPRATHE, Bradley, William**; c/o 3915 Research Park Drive, Suite A-1, Ann Arbor, MI 48108 (US). **BOLTON, Gary**; c/o 3915 Research Park Drive, Suite A-1, Ann Arbor, MI 48108 (US). **KORNBERG, Brian**; c/o 3915 Research Park Drive, Suite A-1, Ann Arbor, MI 48108 (US).

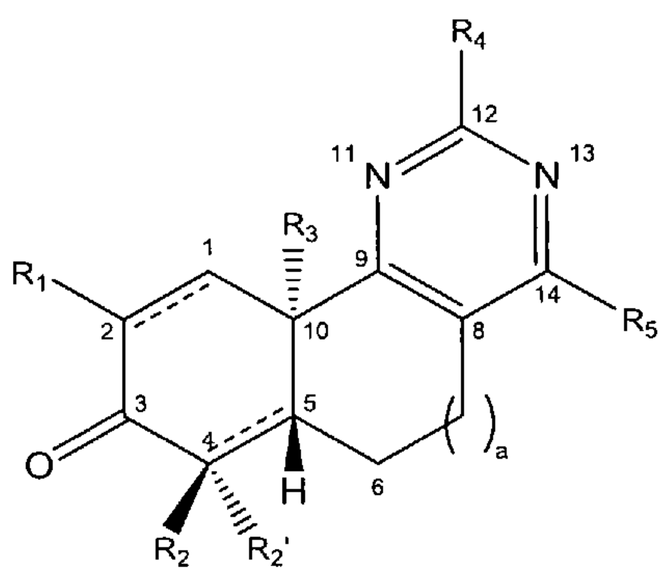
(74) Agent: **LONG, S., Reid**; Parker Highlander PLLC, 1120 S. Capital of Texas Highway, Building One, Suite 200, Austin, TX 78746 (US).

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(54) Title: PYRIMIDINE TRICYCLIC ENONE DERIVATIVES FOR INHIBITION OF RORγ AND OTHER USES



(I)

(57) Abstract: Disclosed herein are compounds of the formulas: as well as analogs thereof, wherein the variables are defined herein. Also provided are pharmaceutical compositions thereof. In some aspects, the compounds and compositions provided herein may be used to inhibit RORγ and/or reduce the expression of IL-17. Also provided are methods of administering compounds and composition provided herein to a patient in need thereof, for example, for the treatment or prevention of diseases or disorders associated with inflammation or autoimmune disorders.

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JUMBO APPLICATIONS/PATENTS

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PYRIMIDINE TRICYCLIC ENONE DERIVATIVES FOR INHIBITION OF RORγ AND OTHER USES

This application claims the benefit of priority to United States Provisional Application No. 62/435,588, filed on December 16, 2016, the entire contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of biology and medicine. More particularly, it concerns compounds, compositions, and methods for the treatment and prevention of diseases such as those associated with RAR-related orphan receptor γ (RORγ) and excess production of IL-17.

II. Description of Related Art

Inflammatory diseases, particularly autoimmune diseases, such as rheumatoid arthritis, osteoarthritis, psoriasis, and multiple sclerosis, frequently have severe and long-term adverse effects on a patient's physical well-being and quality of life. In many patients these diseases cause significant disability, and in some cases (*e.g.*, lupus and multiple sclerosis), they may be life-threatening. Recent advances in therapeutic options, such as the development of therapeutic antibodies against tumor necrosis factor (TNF), have improved outcomes and quality of life for many patients. However, significant numbers of patients do not achieve adequate relief of symptoms from these therapies or cannot tolerate them. Even in patients who do respond, side effects can be significant and may be life-threatening due to immune suppression or other complications.

Recent research on chronic inflammation and autoimmunity has revealed an important role played by a subpopulation of T lymphocytes known as Th17 cells. These cells produce the inflammatory cytokine interleukin 17 (IL-17). Excessive levels of IL-17 have been reported in a variety of autoimmune diseases including multiple sclerosis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases, vitiligo, Sjögren syndrome, and ankylosing spondylitis (Miossec and Kolls, 2012; Yang *et al.*, 2014; Gaffen *et al.*, 2014). Evidence suggests that IL-17 also plays a significant role in the pathology of vasculitis, atherosclerosis, and inflammatory lung diseases, such as cystic fibrosis and chronic obstructive pulmonary disease (COPD). IL-17 is also implicated in the pathophysiology of epilepsy and neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and ALS. Elevated levels of IL-17 or Th17 cells have been reported in patients with psychiatric and neuropsychiatric conditions including schizophrenia, obsessive-compulsive disorder, bipolar disorder, post-traumatic stress disorder, major depression, and autism. Elevations in IL-17 have been implicated in other conditions involving dysregulated inflammatory signaling, including obesity, insulin resistance, and fatty liver disease.

Although Th17 cells are not the only source of IL-17, it has been reported that these cells are a major source of this cytokine in tissues undergoing damage from autoimmune disease, such as arthritic

joints. And elevated levels of IL-17 have been reported to promote tissue degradation, *e.g.*, by stimulating the production of matrix metalloproteinases (a source of damage to connective tissue and cartilage) and increasing the expression of receptor activator of NF-κB ligand (RANKL), which stimulates osteoclast activity and promotes bone damage.

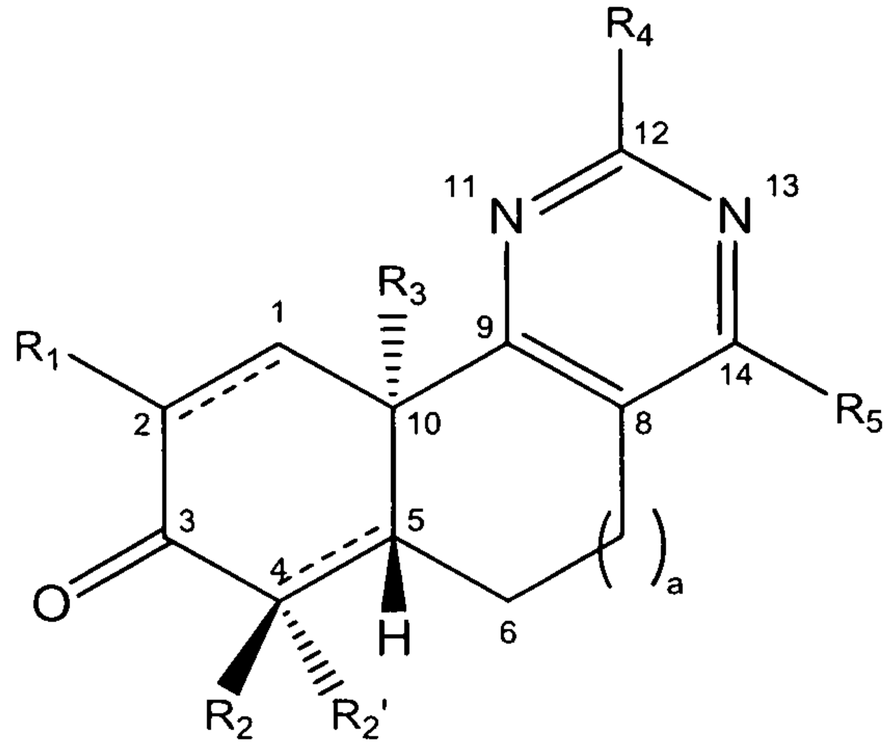
Inappropriate activity of Th17 cells, including overproduction of IL-17, has also been implicated in the pathologies associated with certain viral and parasitic infections. For example, IL-17 has been implicated in the development of severe neuroinflammation associated with *Toxoplasma gondii* infection and increased severity of lesions associated with *Leishmania* infection. In these and other cases, IL-17 appears to play a role in perpetuating the infection, promoting an excessive inflammatory response, and inhibiting clearance of the infectious agent (Waite and Skokos, 2011). Accordingly, therapies that prevent or inhibit excess production of IL-17, or otherwise reduce circulating levels of IL-17, would have significant potential in a wide range of diseases or disorders, including those with inflammatory and autoimmune-related components.

Both the differentiation of Th17 cells and their production of IL-17 are regulated to a significant degree by the RAR-related orphan receptor RORγt, a member of the nuclear hormone receptor family. Expression of RORγt is common to all types of Th17 cells and plays a significant role in their differentiation as well as their activity. RORγ also regulates the production of IL-17 in other cell types, including gamma delta T cells, innate lymphoid cells, and lymphoid tissue inducer cells (Bronner *et al.*, 2016). Inhibition of RORγt activity has been shown to result in reduced expression of IL-17. As such, the identification and synthesis of small molecule inhibitors of RORγt is of great interest.

SUMMARY OF THE INVENTION

The present disclosure provides novel compounds, including pyrimidinyl tricyclic enone derivatives with anti-inflammatory and/or antioxidant properties, pharmaceutical compositions thereof, methods for their manufacture, and methods for their use, including for the inhibition of RORγ nuclear receptor the prevention and treatment of diseases or disorders associated with and/or IL-17 overproduction of IL-17.

In some aspects, the present disclosure provides compounds of the formula:



(I)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of these groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, alkyl$_{(C\leq 18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted

heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, amido$_{(C\leq 18)}$, substituted amido$_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

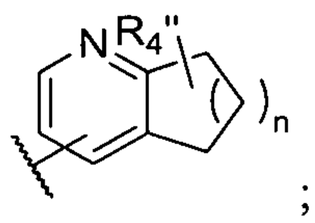
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

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

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, $-C(O)-$alkoxy$_{(C\leq 8)}$, $-C(O)-$alkylamino$_{(C\leq 8)}$, $-C(O)-$dialkyl-amino$_{(C\leq 8)}$, alkylsulfonyl$_{(C\leq 8)}$, arylsulfonyl$_{(C\leq 8)}$, alkoxysulfonyl$_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4''';$$

wherein:

X_2 is arenediyl$_{(C\leq 12)}$, substituted arenediyl$_{(C\leq 12)}$, heterocycloalkanediyl$_{(C\leq 12)}$, substituted heterocycloalkanediyl$_{(C\leq 12)}$, heteroarenediyl$_{(C\leq 12)}$, or substituted heteroarenediyl$_{(C\leq 12)}$;

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

R_4''' is alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, $-C(O)-$alkoxy$_{(C\leq 8)}$, $-C(O)-$alkylamino$_{(C\leq 8)}$, $-C(O)-$dialkyl-amino$_{(C\leq 8)}$, alkylsulfonyl$_{(C\leq 8)}$, arylsulfonyl$_{(C\leq 8)}$, alkoxysulfonyl$_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, alkyl$_{(C\leq 12)}$, alkoxy$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, cycloalkoxy$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, heterocycloalkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, acyloxy$_{(C\leq 12)}$, alkylamino$_{(C\leq 12)}$, dialkylamino$_{(C\leq 12)}$, alkylsulfonylamino$_{(C\leq 12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$; or

$-Y_2-C(O)NR_c-A_2$;

wherein:

Y_2 is arenediyl$_{(C\leq 8)}$ or substituted arenediyl$_{(C\leq 8)}$;

R_c is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

A_2 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$; or

$-A_3R_d$;

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

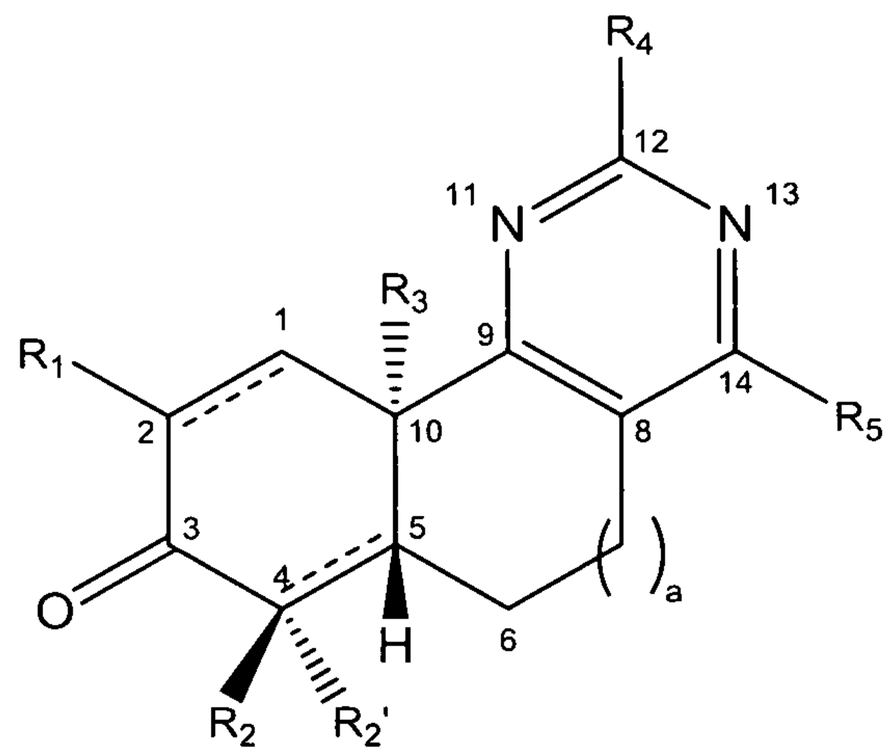
R_e is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

R_d is acyl$_{(C\leq 12)}$, or substituted acyl$_{(C\leq 12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the present disclosure provides compounds of the formula:



(I)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of these

groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $alkyl_{(C\leq18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

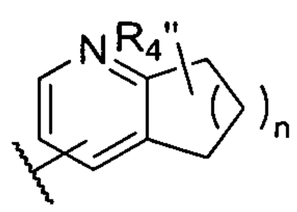
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4''';$$

wherein:

X_2 is $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$,

alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, or a substituted version of any of the last eleven groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$; or

$$-Y_2-C(O)NR_c-A_2;$$

wherein:

Y_2 is arenediyl$_{(C\leq8)}$ or substituted arenediyl$_{(C\leq8)}$;

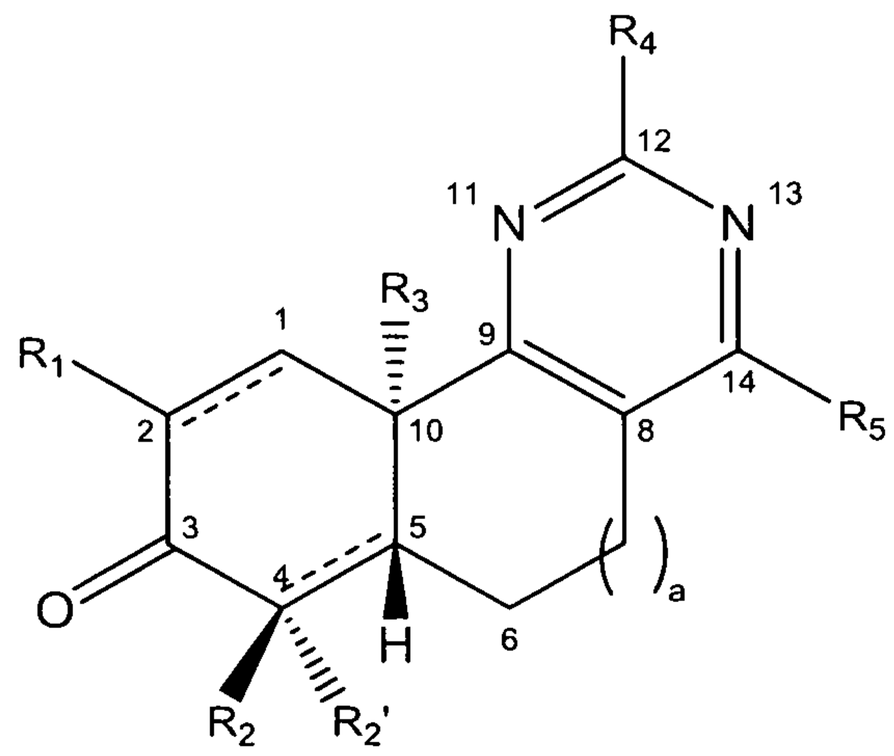
R_c is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

A_2 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$; or

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(I)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq8)}$, substituted heteroaryl$_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, dialkylamino$_{(C\leq8)}$, alkylsulfonylamino$_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq8)}-$cycloalkyl$_{(C\leq12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, or a substituted version of these

groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

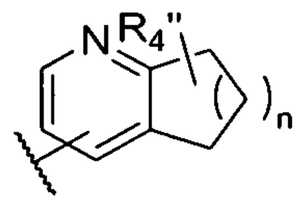
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4''';$$

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$-OY_1-A_1$;

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$-Y_2-C(O)NR_c-A_2$;

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_c is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$-A_3R_d$;

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

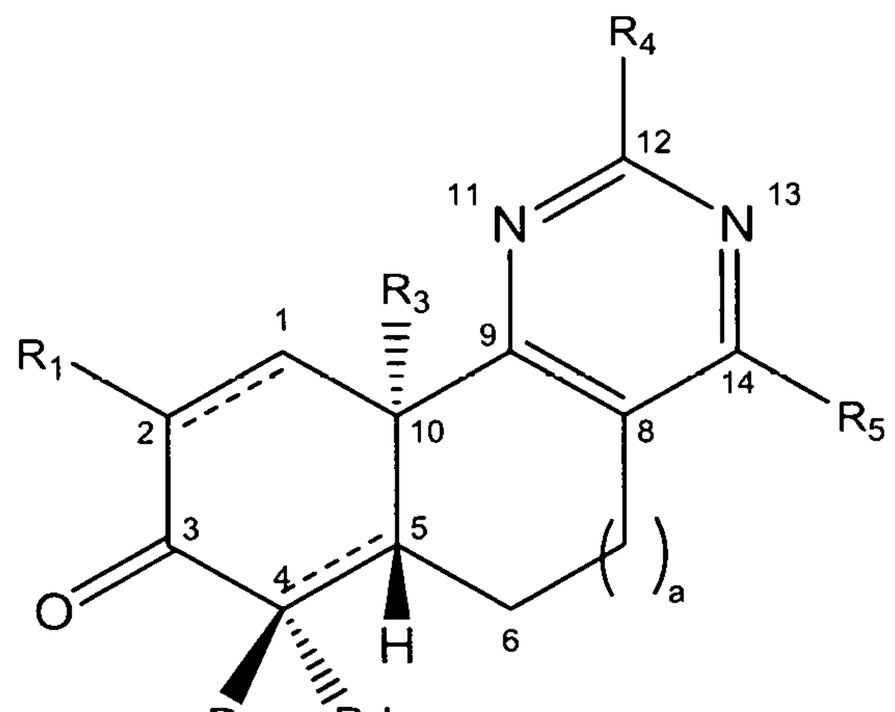
R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the compounds are further defined as:



(I)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of these groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

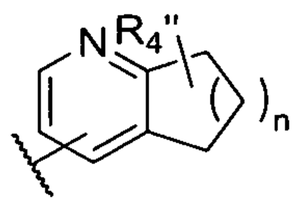
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4''';$$

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_c-A_2;$$

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_c is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d;$$

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

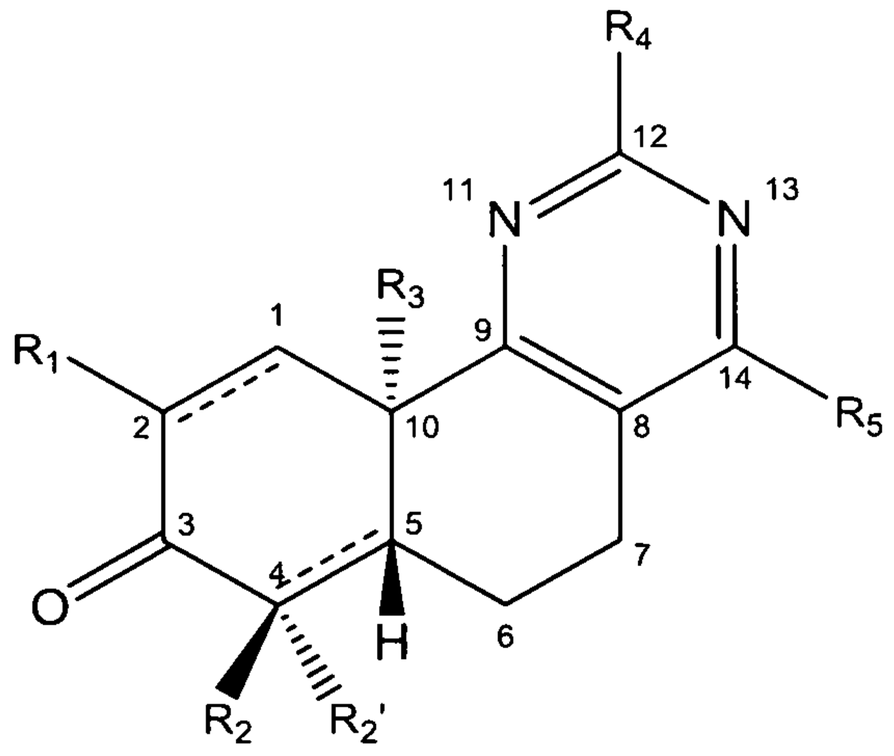
R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(II)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, alkyl$_{(C2\text{-}18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, alkylamino$_{(C\leq 18)}$, substituted alkylamino$_{(C\leq 18)}$, dialkylamino$_{(C\leq 18)}$, substituted dialkylamino$_{(C\leq 18)}$, alkylthio$_{(C\leq 18)}$, substituted alkylthio$_{(C\leq 18)}$, amido$_{(C\leq 18)}$, substituted amido$_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

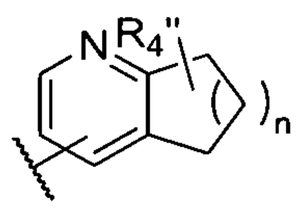
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

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

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, $-C(O)-$alkoxy$_{(C\leq 8)}$, $-C(O)-$alkylamino$_{(C\leq 8)}$, $-C(O)-$dialkyl-amino$_{(C\leq 8)}$,

alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is arenediyl$_{(C\leq12)}$, substituted arenediyl$_{(C\leq12)}$, heterocycloalkanediyl$_{(C\leq12)}$, substituted heterocycloalkanediyl$_{(C\leq12)}$, heteroarenediyl$_{(C\leq12)}$, or substituted heteroarenediyl$_{(C\leq12)}$;

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

R_4''' is alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, amido$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, $-C(O)-$alkoxy$_{(C\leq8)}$, $-C(O)-$alkylamino$_{(C\leq8)}$, $-C(O)-$dialkyl-amino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, alkyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$; or

$$-Y_2-C(O)NR_c-A_2$$;

wherein:

Y_2 is arenediyl$_{(C\leq8)}$ or substituted arenediyl$_{(C\leq8)}$;

R_c is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

A_2 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$; or

$$-A_3R_d$$;

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

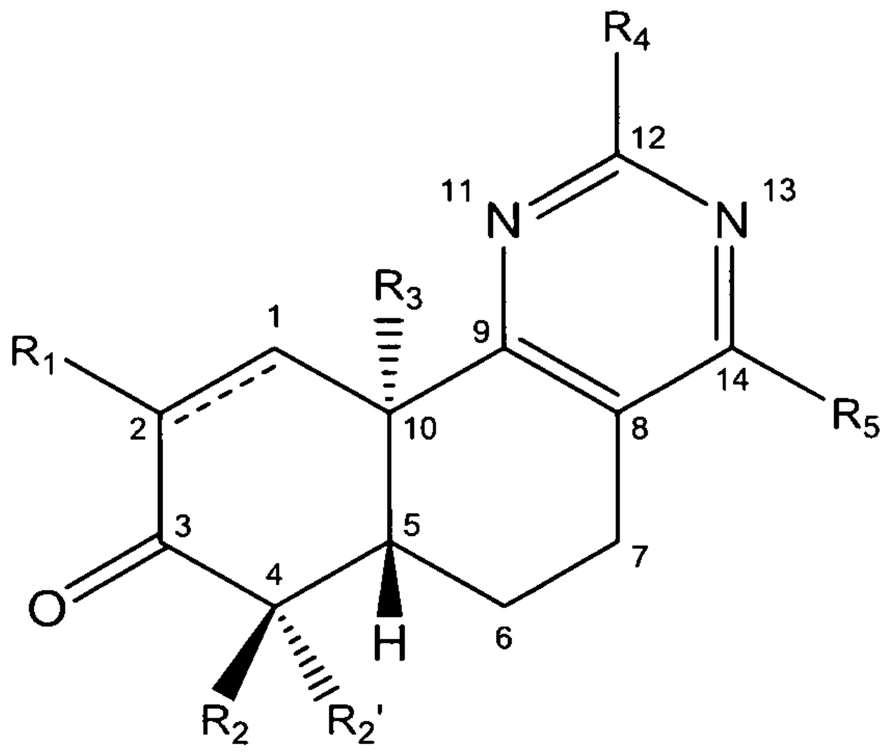
R_e is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

R_d is acyl$_{(C\leq12)}$, or substituted acyl$_{(C\leq12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(III)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups;

R_3 is alkyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, alkyl$_{(C2\text{-}18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, alkylamino$_{(C\leq 18)}$, substituted alkylamino$_{(C\leq 18)}$, dialkylamino$_{(C\leq 18)}$, substituted dialkylamino$_{(C\leq 18)}$, alkylthio$_{(C\leq 18)}$, substituted alkylthio$_{(C\leq 18)}$, amido$_{(C\leq 18)}$, substituted amido$_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

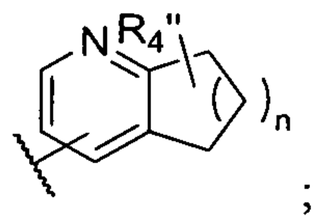
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

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

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d$$;

wherein:

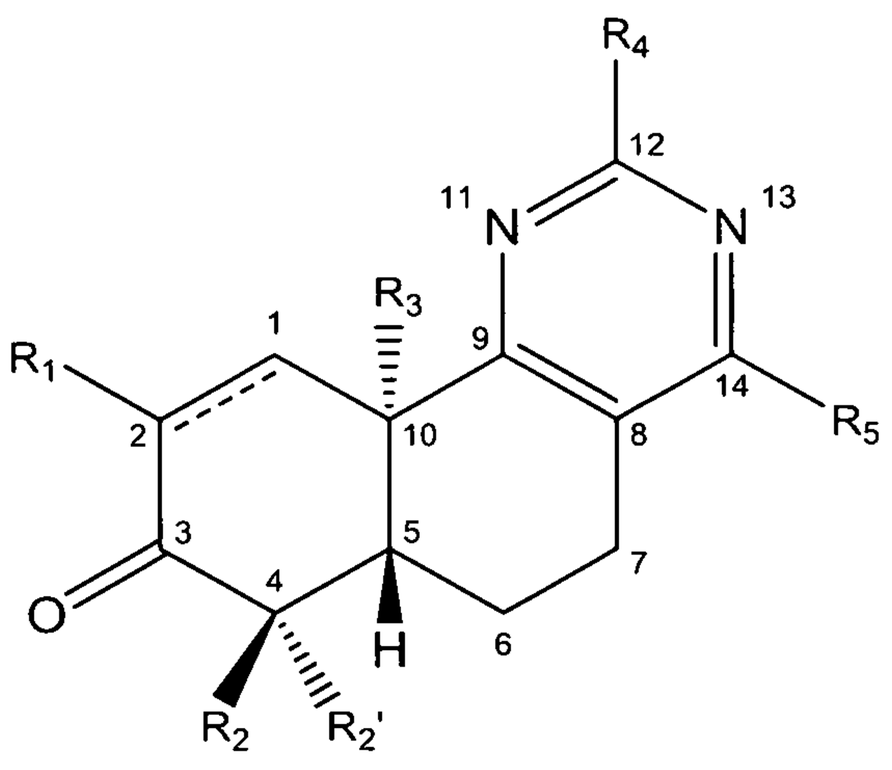
A_3 is −O− or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the compounds are further defined as:



(III)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_2' is hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, or a substituted version of the last four groups;

R_3 is $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

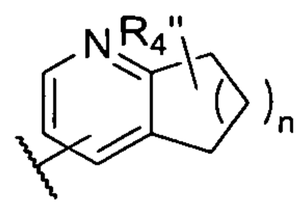
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d$$;

wherein:

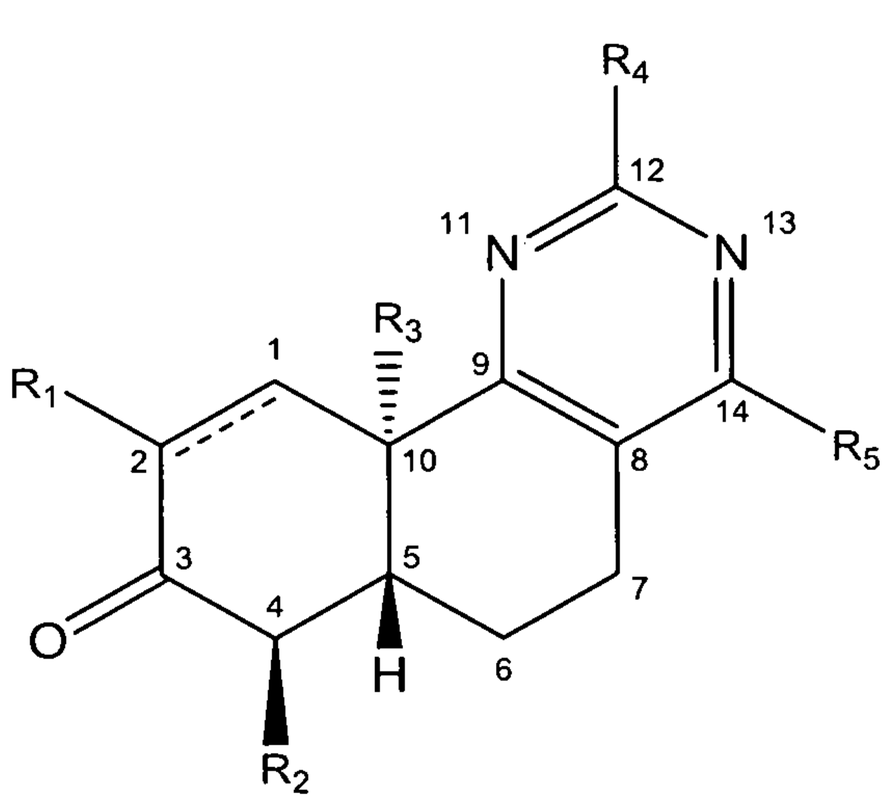
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(IV)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_3 is $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

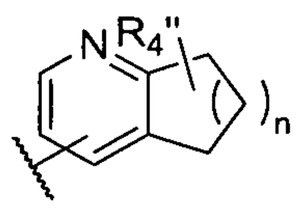
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d$$;

wherein:

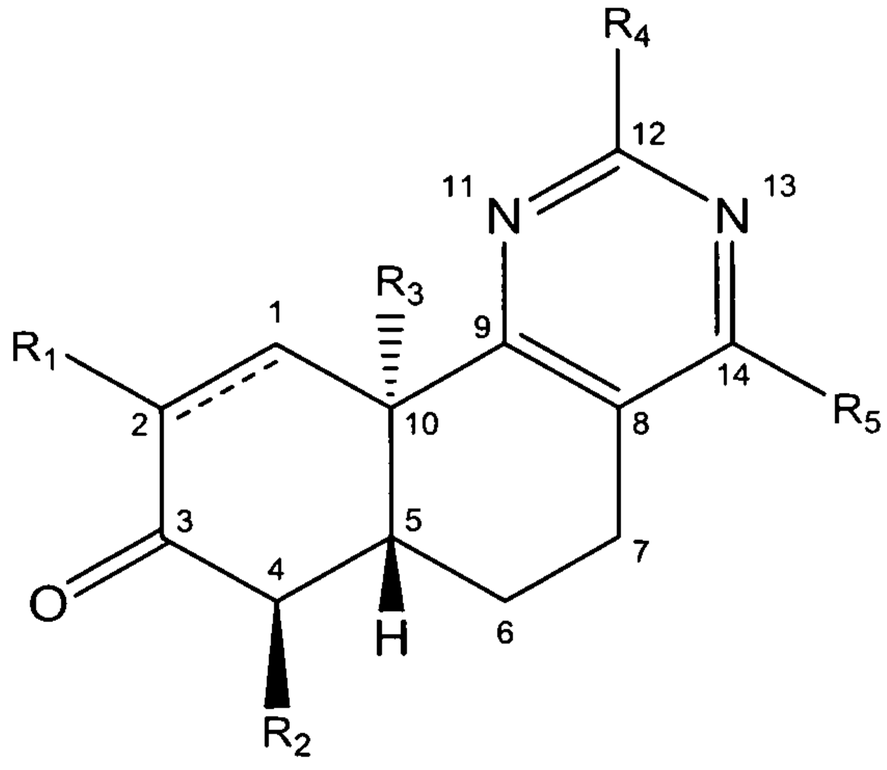
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the compounds are further defined as:



(IV)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_3 is $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

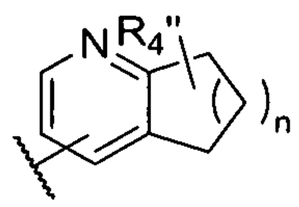
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $cycloalkyl_{(C\leq 18)}$, $aryl_{(C\leq 18)}$, $aralkyl_{(C\leq 18)}$, $heteroaryl_{(C\leq 18)}$, $heteroaralkyl_{(C\leq 18)}$, $heterocycloalkyl_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq 12)}$, substituted $arenediyl_{(C\leq 12)}$, $heterocycloalkanediyl_{(C\leq 12)}$, substituted $heterocycloalkanediyl_{(C\leq 12)}$, $heteroarenediyl_{(C\leq 12)}$, or substituted $heteroarenediyl_{(C\leq 12)}$;

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

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq 8)}$ or substituted $arenediyl_{(C\leq 8)}$;

R_b is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

A_2 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$; or

$$-A_3R_d$$;

wherein:

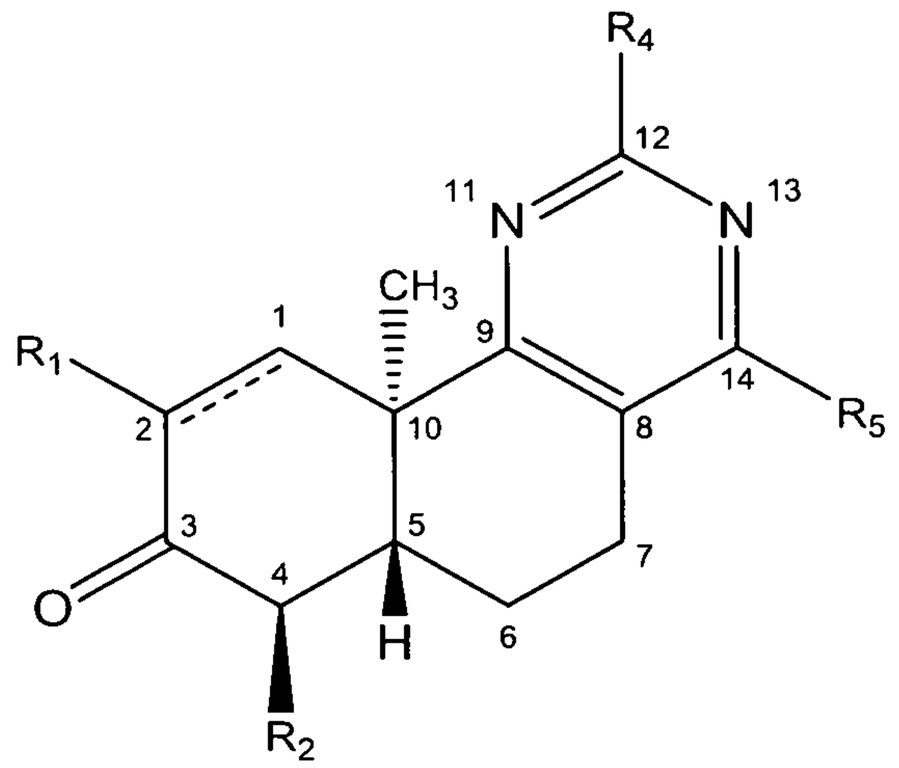
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(V)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

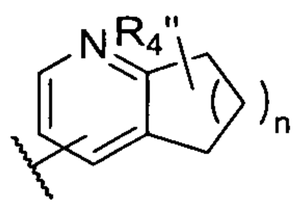
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 18)}$, $aryl_{(C\leq 18)}$, $aralkyl_{(C\leq 18)}$, $heteroaryl_{(C\leq 18)}$, $heteroaralkyl_{(C\leq 18)}$, $heterocycloalkyl_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$

wherein:

X_2 is $arenediyl_{(C\leq 12)}$, substituted $arenediyl_{(C\leq 12)}$, $heterocycloalkanediyl_{(C\leq 12)}$, substituted $heterocycloalkanediyl_{(C\leq 12)}$, $heteroarenediyl_{(C\leq 12)}$, or substituted $heteroarenediyl_{(C\leq 12)}$;

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

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

$$-Y_2-C(O)NR_b-A_2;$$

wherein:

Y_2 is $arenediyl_{(C\leq 8)}$ or substituted $arenediyl_{(C\leq 8)}$;

R_b is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

A_2 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$; or

$$-A_3R_d;$$

wherein:

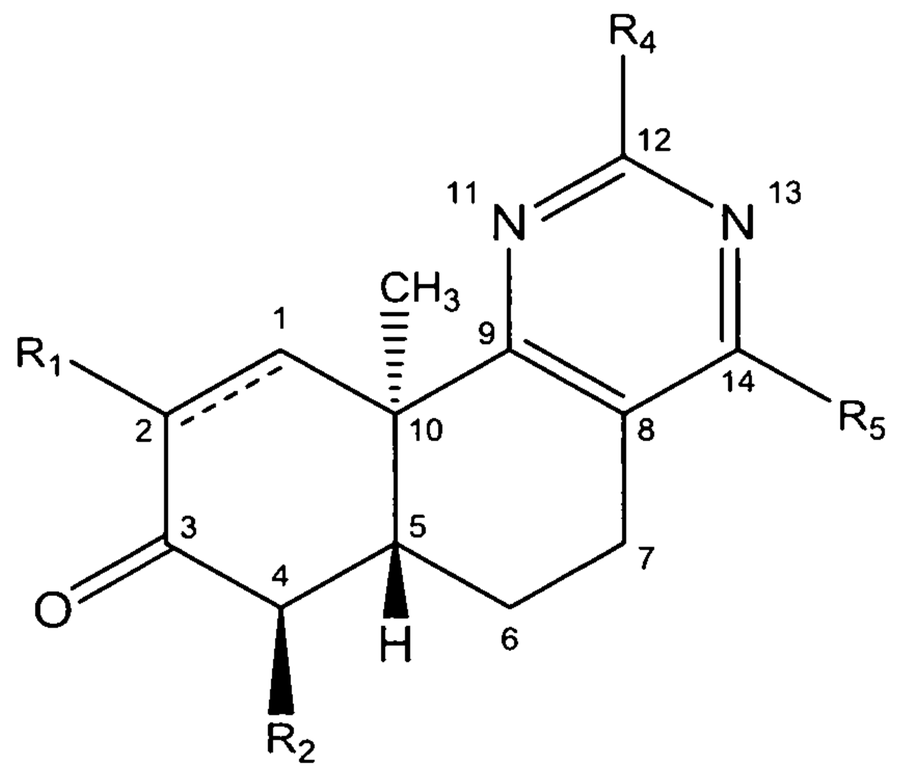
A_3 is –O– or –NR_e–, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the compounds are further defined as:



(V)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $–CF_3$, or –C(O)R_a; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or –$alkanediyl_{(C\leq8)}$–$cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$–X_1–(CH_2)_m–R_4';$$

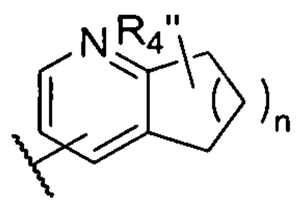
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d$$;

wherein:

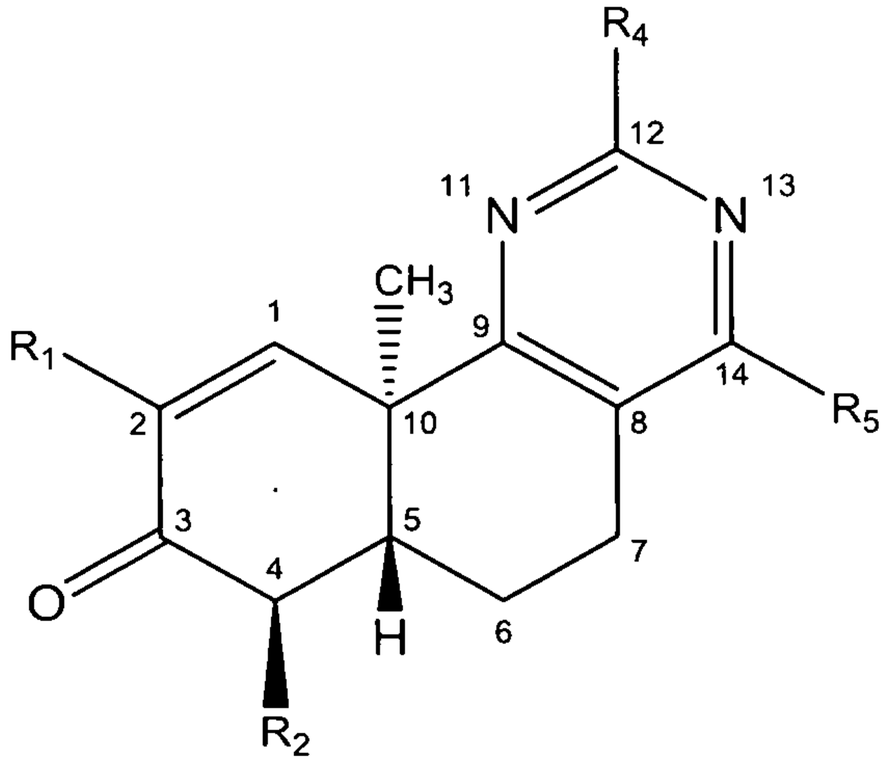
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(VI)

wherein:

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$-X_1-(CH_2)_m-R_4'$;

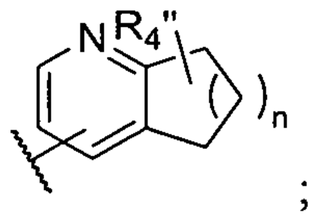
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d$$;

wherein:

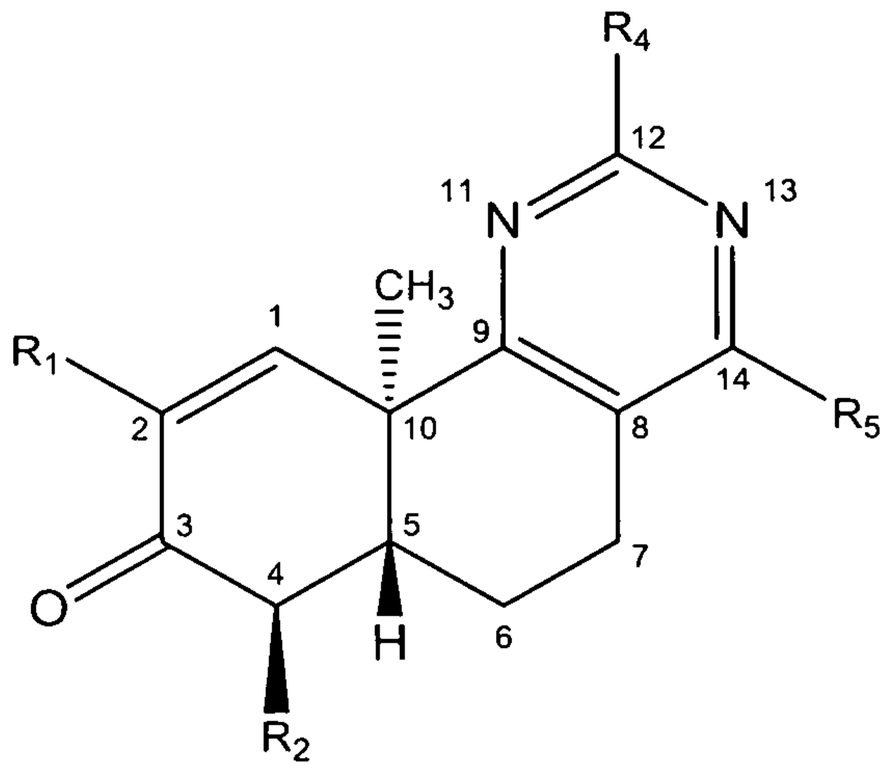
A_3 is −O− or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the compounds are further defined as:



(VI)

wherein:

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

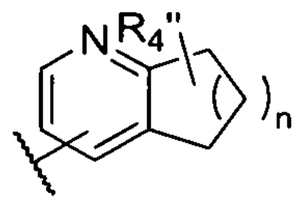
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2;$$

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d;$$

wherein:

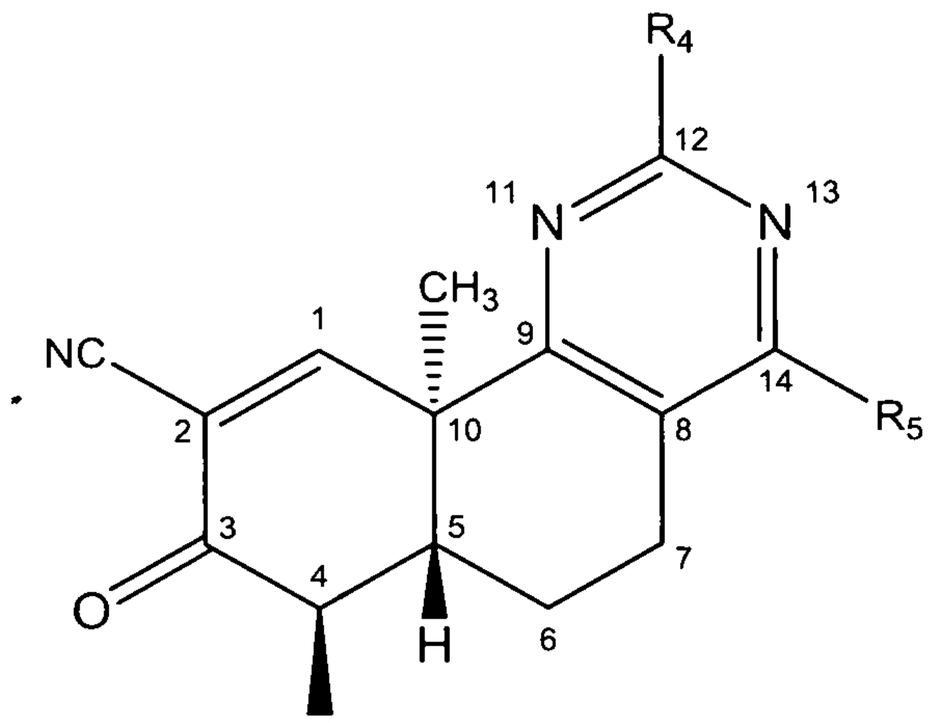
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



R2

(VII)

wherein:

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

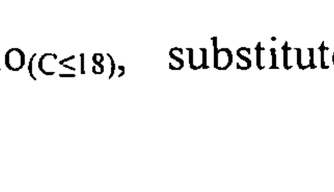
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$,

$-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq 12)}$, substituted $arenediyl_{(C\leq 12)}$, $heterocycloalkanediyl_{(C\leq 12)}$, substituted $heterocycloalkanediyl_{(C\leq 12)}$, $heteroarenediyl_{(C\leq 12)}$, or substituted $heteroarenediyl_{(C\leq 12)}$;

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

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq 8)}$ or substituted $arenediyl_{(C\leq 8)}$;

R_b is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

A_2 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$; or

$$-A_3R_d$$;

wherein:

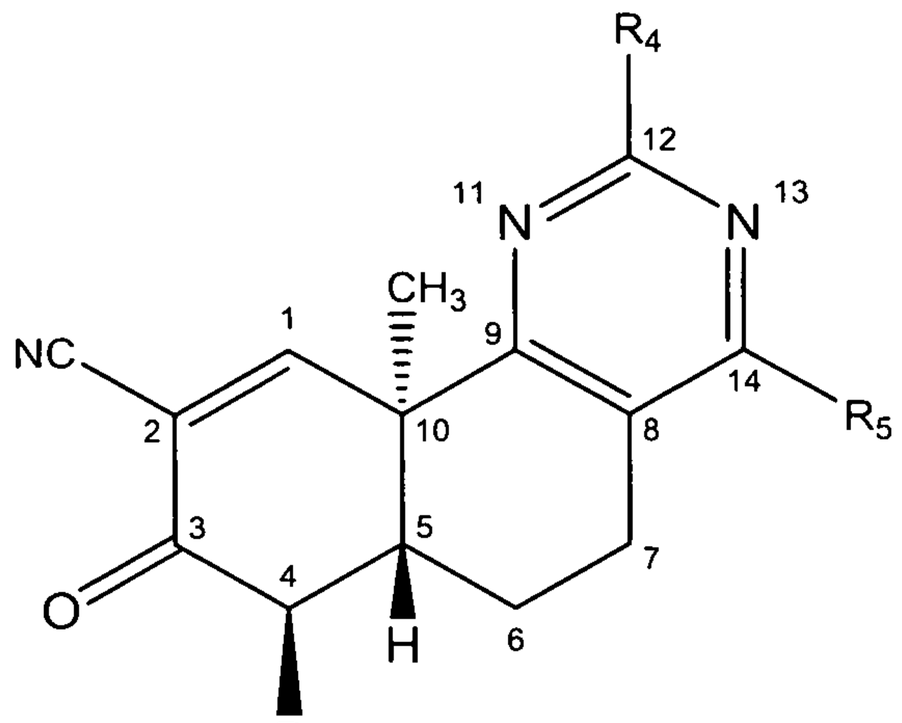
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the compounds are further defined as:



R_2

(VII)

wherein:

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

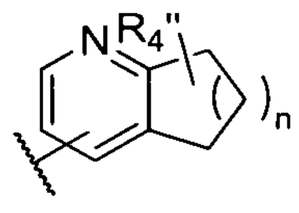
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$,

alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is arenediyl$_{(C\leq12)}$, substituted arenediyl$_{(C\leq12)}$, heterocycloalkanediyl$_{(C\leq12)}$, substituted heterocycloalkanediyl$_{(C\leq12)}$, heteroarenediyl$_{(C\leq12)}$, or substituted heteroarenediyl$_{(C\leq12)}$;

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

R_4''' is alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, $-C(O)-$alkoxy$_{(C\leq8)}$, $-C(O)-$alkylamino$_{(C\leq8)}$, $-C(O)-$dialkyl-amino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, alkyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is arenediyl$_{(C\leq8)}$ or substituted arenediyl$_{(C\leq8)}$;

R_b is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

A_2 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$; or

$$-A_3R_d$$;

wherein:

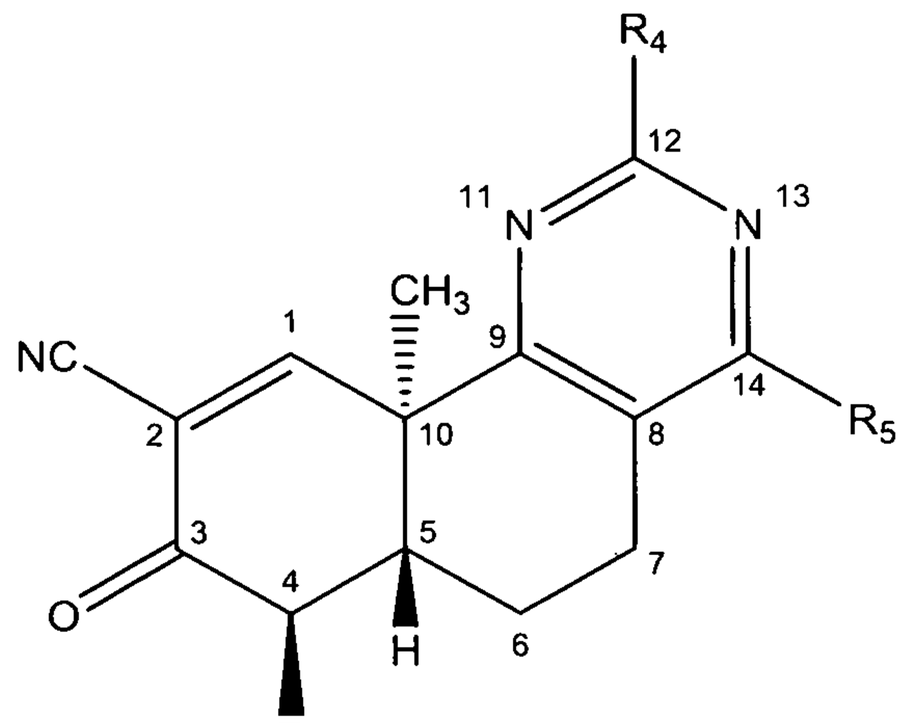
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

R_d is acyl$_{(C\leq12)}$, or substituted acyl$_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(VII)

wherein:

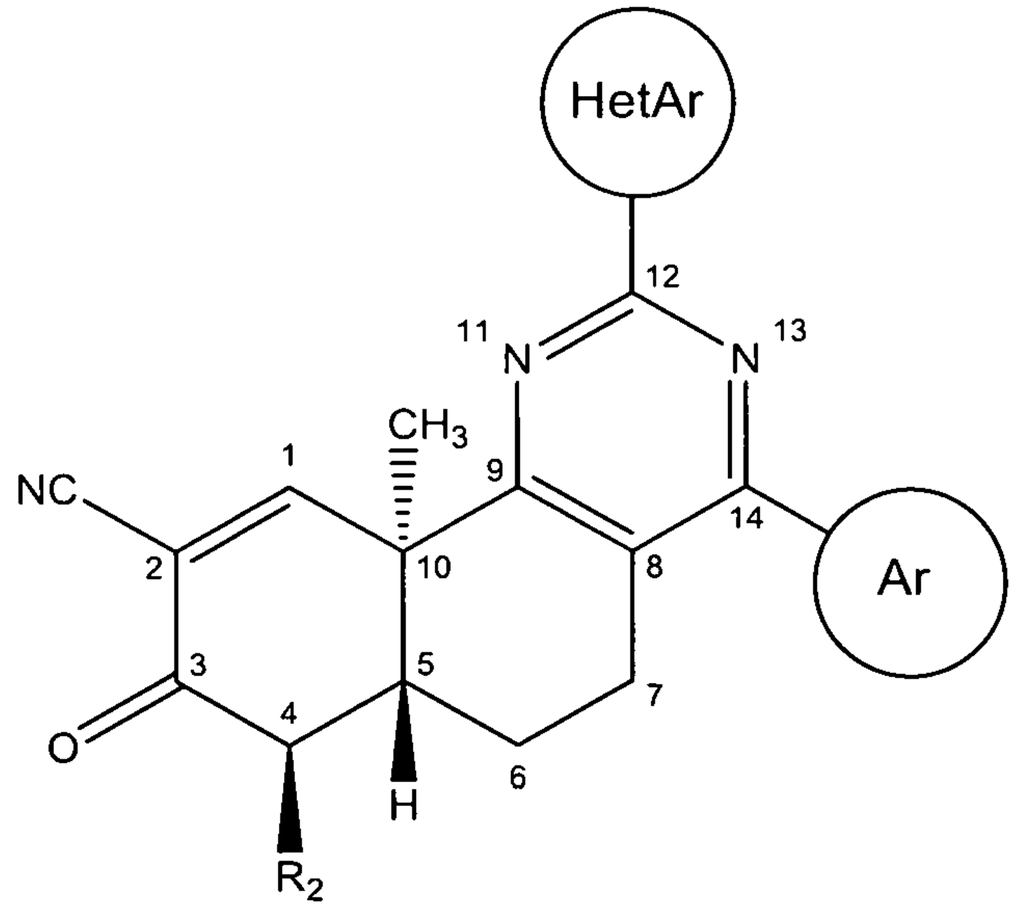
R_2 is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$;

R_4 is $heteroaryl_{(C\leq18)}$ or substituted $heteroaryl_{(C\leq18)}$; and

R_5 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(VIII)

wherein:

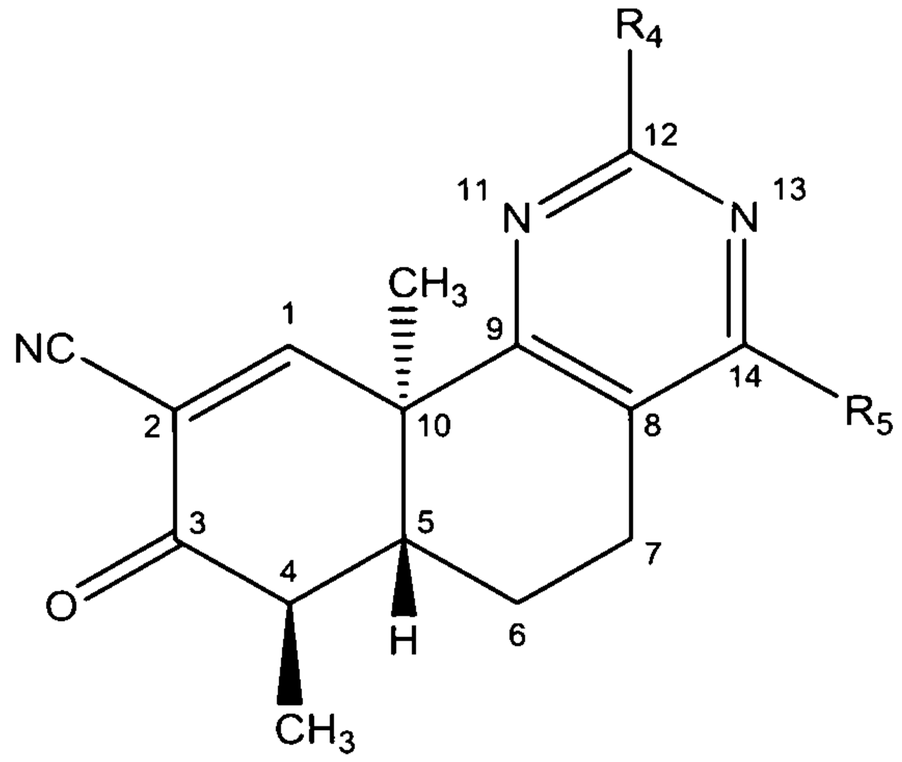
R_2 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$;

HetAr is $heteroaryl_{(C\leq18)}$ or substituted $heteroaryl_{(C\leq18)}$; and

Ar is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



(IX)

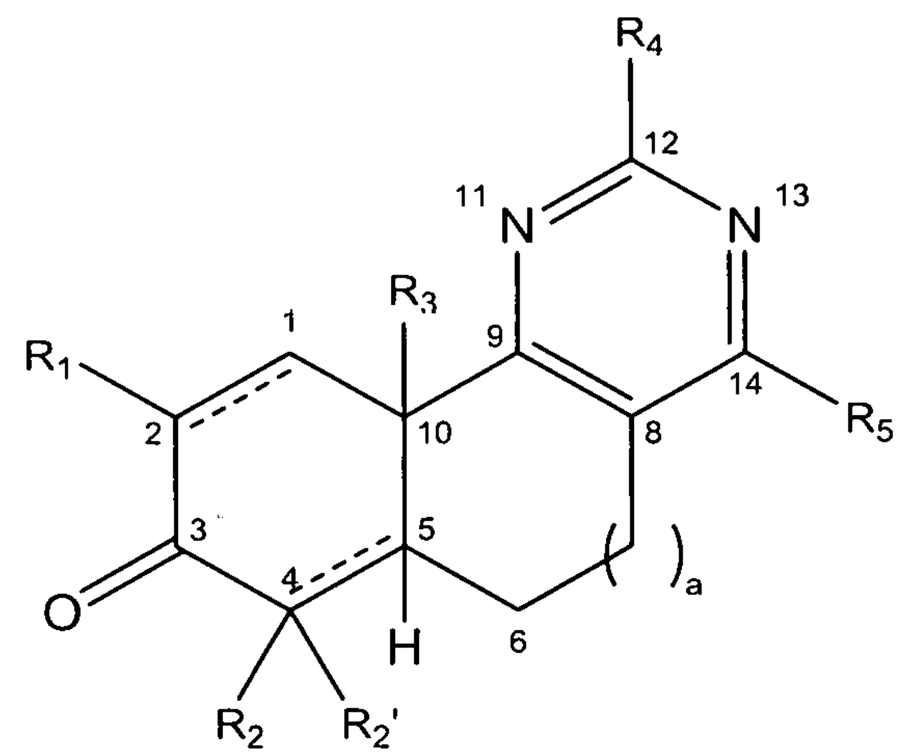
wherein:

R_4 is heteroaryl$_{(C\leq 18)}$ or substituted heteroaryl$_{(C\leq 18)}$; and

R_5 is aryl$_{(C\leq 12)}$ or substituted aryl$_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the present disclosure provides compounds of the formula:



(X)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, or a substituted version of the last four groups, provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

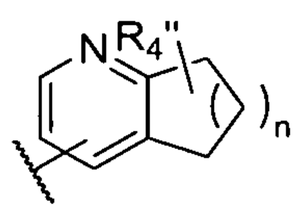
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is –H, –OH, –F, –Cl, –Br, –I, $-NH_2$, $-NO_2$, –CN, –SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4''';$$

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, or a substituted version of any of the last three groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$; or

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the bond between carbon atom 1 and carbon atom 2 is an epoxidized double bond. In other embodiments, the bond between carbon atom 1 and carbon atom 2 is a double bond. In some embodiments, the bond between carbon atom 4 and carbon atom 5 is a single bond. In other embodiments, the bond between carbon atom 4 and carbon atom 5 is a double bond. In some embodiments, a is 1. In some embodiments, R_1 is cyano.

In some embodiments, R_2 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$. In some embodiments, R_2 is alkyl$_{(C\leq 12)}$ such as methyl, ethyl, or propyl. In some embodiments, R_2 is methyl. In some embodiments, R_2 is substituted alkyl$_{(C\leq 12)}$ such as 3-hydroxypropyl. In other embodiments, R_2 is alkenyl$_{(C\leq 12)}$ or substituted alkenyl$_{(C\leq 12)}$. In some embodiments, R_2 is alkenyl$_{(C\leq 12)}$ such as 2-propenyl. In some embodiments, R_2' is hydrogen. In other embodiments, R_2' is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$. In some embodiments, R_2' is alkyl$_{(C\leq 12)}$ such as methyl.

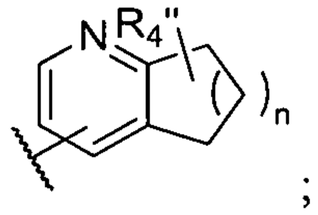
In some embodiments, R_3 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$. In some embodiments, R_3 is alkyl$_{(C\leq 12)}$ such as methyl, propyl, or isopentyl. In some embodiments, R_3 is methyl. In other embodiments, R_3 is aryl$_{(C\leq 12)}$ or substituted aryl$_{(C\leq 12)}$. In some embodiments, R_3 is aryl$_{(C\leq 12)}$ such as phenyl.

In some embodiments, R_4 is alkyl$_{(C2\text{-}18)}$ or substituted alkyl$_{(C2\text{-}18)}$. In other embodiments, R_4 is heteroaryl$_{(C\leq 18)}$ or substituted heteroaryl$_{(C\leq 18)}$. In some embodiments, R_4 is a heteroaryl$_{(C\leq 12)}$ or a substituted heteroaryl$_{(C\leq 12)}$ group wherein at least one of the heteroatoms in the aromatic ring is a nitrogen atom. In some embodiments, R_4 is heteroaryl$_{(C\leq 18)}$ such as 3-pyridinyl, 4-pyridinyl, 4-(2-cycylopropyl)-pyridinyl, 5-(2-cycylopropyl)-pyridinyl, 4-(2-morpholino)-pyridinyl, 4-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 3-(6-methyl)-pyridinyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-pyrazolo[1,5-*a*]pyridinyl, 3-(*N*-methyl)-pyrrolo[2,3-*b*]pyridinyl, 5-isoquinlinyl, 2-isoquinlinyl, 1-isoquinolinyl, 4-(2-phenyl)-pyridinyl, 5-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 4-(3,5-dimethyl)-isoxazolyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-(4-methyl)-pyridinyl, 4-(6-methyl)-pyrimidinyl, 6-(4-methyl)-pyrimidinyl, 4-pyridazinyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 5-quinolinyl, 6-quinolinyl, 8-quinolinyl, 4-isoquinolinyl, 3-(8-methyl)-quinolinyl, 3-(1-methyl)-quinolinyl, 4-(2-methyl)-quinolinyl, 4-(2-isopropyl)-quinolinyl, 4-(6-methyl)-quinolinyl, 4-(7-methyl)-quinolinyl, 4-(8-methyl)-quinolinyl, 2-(*N*-methyl)-indolyl, 5-(2,4-dimethyl)-thiazolyl, or 5-(3-methyl)-oxadizolyl. In other embodiments, R_4 is substituted heteroaryl$_{(C\leq 18)}$ such as 4-(2-trifluoromethyl)-pyridinyl, 4-(3-fluoro)-pyridinyl, 4-(2-methoxy)-pyridinyl, 4-(2-hydroxymethyl)-pyridinyl, 4-(2-acetylamino)-pyridinyl, 4-(2-fluoromethyl)-pyridinyl, 4-(2-acetamidylethyl)-pyridinyl, 4-(2-fluoromethyl)-quinolinyl, 4-(2-acetoxymethyl)-quinolinyl, 4-(2-formyl)-

quinolinyl, 4-(6-fluoro)-quinolinyl, 4-(7-fluoro)-quinolinyl, 4-(8-fluoro)-quinolinyl, 4-(6,8-difluoro)-quinolinyl, 4-(6-fluoro-2-methyl)-quinolinyl, or 4-(8-fluoro-2-methyl)-quinolinyl.

In other embodiments, R_4 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$. In some embodiments, R_4 is $aryl_{(C\leq12)}$ such as phenyl. In other embodiments, R_4 is substituted $aryl_{(C\leq12)}$ such as 2-fluorophenyl or 4-trifluoromethylphenyl. In other embodiments, R_4 is $cycloalkyl_{(C\leq12)}$ or substituted $cycloalkyl_{(C\leq12)}$. In some embodiments, R_4 is $cycloalkyl_{(C\leq12)}$ such as cyclohexyl.

In other embodiments, R_4 is:



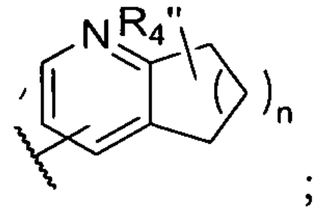
;

wherein:

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

R_4'' is $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups.

In other embodiments, R_4 is:



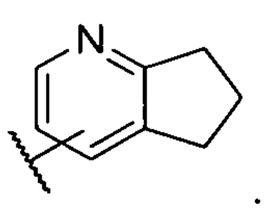
;

wherein:

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

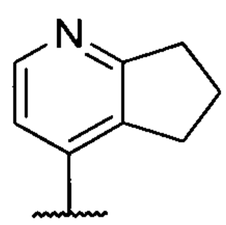
R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups.

In some embodiments, R_4 is:



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In some embodiments, R_4 is:



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In other embodiments, R_4 is heterocycloalkyl$_{(C\leq 18)}$ or substituted heterocycloalkyl$_{(C\leq 18)}$. In some embodiments, R_4 is heterocycloalkyl$_{(C\leq 12)}$ such as morpholinyl, 4-piperidinyl, 3-(5-methyl-)1,2,3,6-tetrahydropyridinyl, or 4-*N*-methylpiperazinyl. In other embodiments, R_4 is substituted heterocycloalkyl$_{(C\leq 12)}$ such as *N*-*t*-butyloxycarbonyl-4-piperidinyl, *N*-acetyl-4-piperidinyl, *N*-*t*-butyloxycarbonyl-5-methyl-1,2,3,6-tetrahydropyridinyl, *N*-acetyl-5-methyl-1,2,3,6-tetrahydropyridinyl, or 4-*N*-acetylpiperazinyl. In other embodiments, R_4 is hydrogen.

In other embodiments, R_4 is $-X_1-(CH_2)_m-R_4'$; wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

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

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl.

In other embodiments, R_4 is $-X_1-(CH_2)_m-R_4'$; wherein:

X_1 is NR_b, O, or S; wherein:

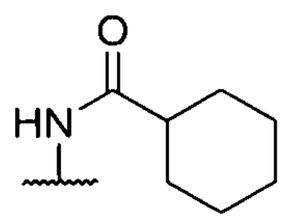
R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

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

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups.

In some embodiments, X_1 is NR_b, wherein: R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$. In some embodiments, R_b is hydrogen. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, R_4' is cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups. In some embodiments, R_4' is heteroaryl$_{(C\leq 12)}$ or substituted heteroaryl$_{(C\leq 12)}$. In some embodiments, R_4' is heteroaryl$_{(C\leq 12)}$ such as 4-pyridinyl.

In other embodiments, R_4 is amino. In other embodiments, R_4 is amido$_{(C\leq 12)}$ or substituted amido$_{(C\leq 12)}$. In some embodiments, R_4 is amido$_{(C\leq 12)}$ such as:



In other embodiment, R_4 is $-X_2-(CH_2)_p-R_4'''$; wherein:

X_2 is arenediyl$_{(C\leq 12)}$, substituted arenediyl$_{(C\leq 12)}$, heterocycloalkanediyl$_{(C\leq 12)}$, substituted heterocycloalkanediyl$_{(C\leq 12)}$, heteroarenediyl$_{(C\leq 12)}$, or substituted heteroarenediyl$_{(C\leq 12)}$;

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

R_4''' is alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, $-C(O)-$alkoxy$_{(C\leq 8)}$, $-C(O)-$alkylamino$_{(C\leq 8)}$,

−C(O)−dialkylamino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups.

In other embodiments, $-X_2-(CH_2)_p-R_4'''$; wherein:

X_2 is heterocycloalkanediyl$_{(C\leq12)}$, substituted heterocycloalkanediyl$_{(C\leq12)}$, heteroarenediyl$_{(C\leq12)}$, or substituted heteroarenediyl$_{(C\leq12)}$;

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

R_4''' is alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, −C(O)−alkoxy$_{(C\leq8)}$, −C(O)−alkylamino$_{(C\leq8)}$, −C(O)−dialkylamino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups.

In some embodiments, X_2 is heteroarenediyl$_{(C\leq12)}$ or substituted heteroarenediyl$_{(C\leq12)}$. In some embodiments, X_2 is heteroarenediyl$_{(C\leq12)}$ such as pyridin-2,4-diyl or pyridine-2,5-diyl. In other embodiments, X_2 is heterocycloalkanediyl$_{(C\leq12)}$ or substituted heterocycloalkanediyl$_{(C\leq12)}$. In some embodiments, X_2 is heterocycloalkanediyl$_{(C\leq12)}$ such as piperidin-1,4-diyl, piperazin-1,4-diyl, or 1,2,3,6-tetrahydropiperidin-1,5-diyl. In some embodiments, p is 0, 1, or 2. In some embodiments, p is 0. In other embodiments, p is 1. In other embodiments, p is 2.

In some embodiments, R_4''' is acyl$_{(C\leq8)}$ or substituted acyl$_{(C\leq8)}$. In some embodiments, R_4''' is acyl$_{(C\leq8)}$ such as acetyl. In other embodiments, R_4''' is amido$_{(C\leq8)}$ or substituted amido$_{(C\leq8)}$. In some embodiments, R_4''' is amido$_{(C\leq8)}$ such as acetamidyl. In other embodiments, R_4''' is substituted acyl$_{(C\leq8)}$ such as carboxy. In other embodiments, R_4''' is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$. In some embodiments, R_4''' is cycloalkyl$_{(C\leq8)}$ such as cyclopropyl. In other embodiments, R_4''' is alkylsulfonyl$_{(C\leq8)}$ or substituted alkylsulfonyl$_{(C\leq8)}$. In some embodiments, R_4''' is alkylsulfonyl$_{(C\leq8)}$ such as $-S(O)_2CH_3$ or $-S(O)_2CH_2CH_3$. In other embodiments, R_4''' is −C(O)−alkoxy$_{(C\leq8)}$ such as −C(O)OEt. In other embodiments, R_4''' is −C(O)−dialkylamino$_{(C\leq8)}$ such as $-C(O)NMe_2$.

In some embodiments, R_5 is aryl$_{(C\leq12)}$ or substituted aryl$_{(C\leq12)}$. In some embodiments, R_5 is aryl$_{(C\leq12)}$ such as phenyl, 4-methylphenyl, 3-isopropylphenyl, 4-isopropylphenyl, 1,3-biphenyl, or 1,4-biphenyl. In other embodiments, R_5 further comprises one or more fluorine atoms. In some embodiments, R_5 is substituted aryl$_{(C\leq12)}$ such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 4-hydroxymethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, or 3,4-dichlorophenyl. In other embodiments, R_5 is cycloalkyl$_{(C\leq12)}$ or substituted cycloalkyl$_{(C\leq12)}$ such as cyclopropyl. In other embodiments, R_5 is cycloalkoxy$_{(C\leq12)}$ or substituted cycloalkoxy$_{(C\leq12)}$ such as cyclobutyloxy, cyclopentyloxy, or cyclohexyloxy. In other embodiments, R_5 is alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, or a substituted version of either of these groups. In some embodiments, R_5 is dialkylamino$_{(C\leq12)}$ or substituted dialkylamino$_{(C\leq12)}$. In some embodiments, R_5 is dialkylamino$_{(C\leq8)}$ or substituted dialkylamino$_{(C\leq8)}$ such as dimethylamino. In other embodiments, R_5 is alkylsulfonylamino$_{(C\leq12)}$ or substituted alkylsulfonylamino$_{(C\leq12)}$ such as methylsulfonylamino. In other embodiments, R_5 is $-OY_1-A_1$;

wherein:

Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$.

In some embodiments, Y_1 is methylene. In some embodiments, A_1 is cyclobutyl. In some embodiments, R_5 is:

In other embodiments, R_5 is $-Y_2-C(O)NR_c-A_2$; wherein:

Y_2 is arenediyl$_{(C\leq8)}$ or substituted arenediyl$_{(C\leq8)}$;

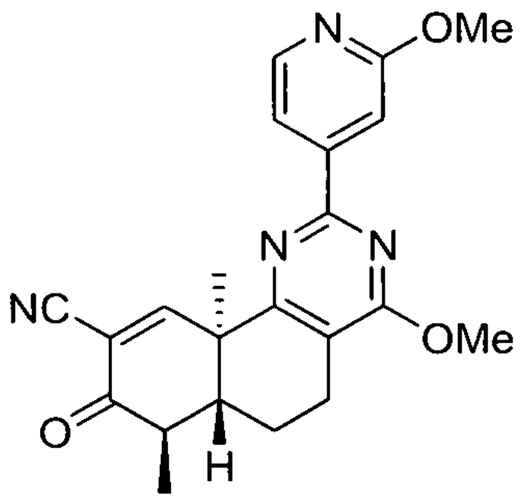
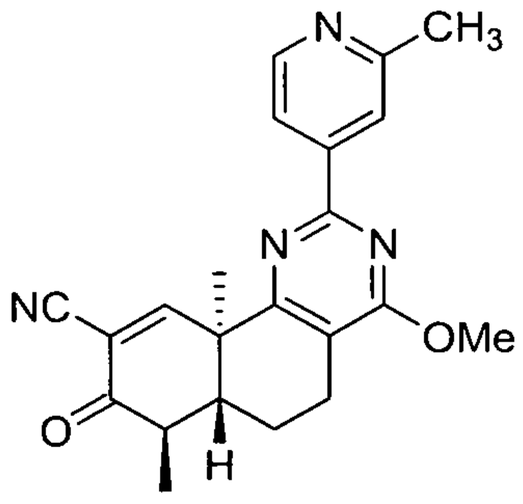
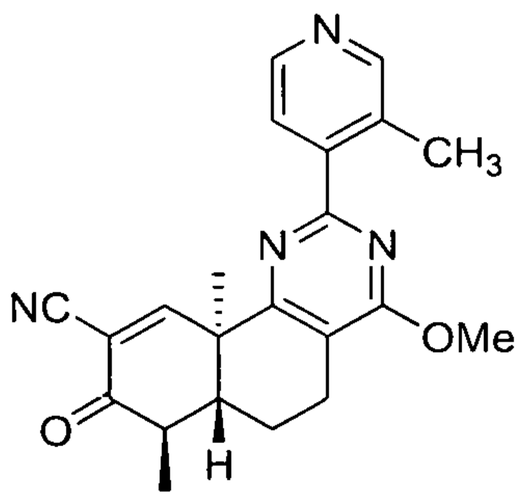
R_c is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

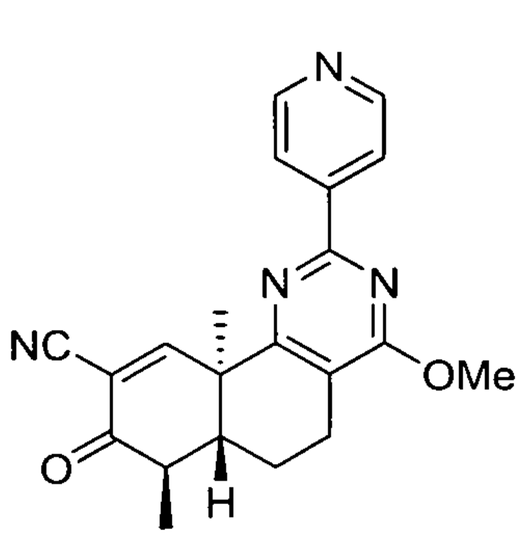
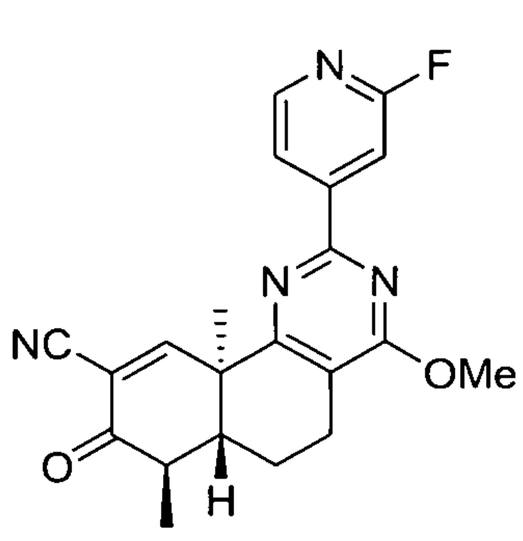
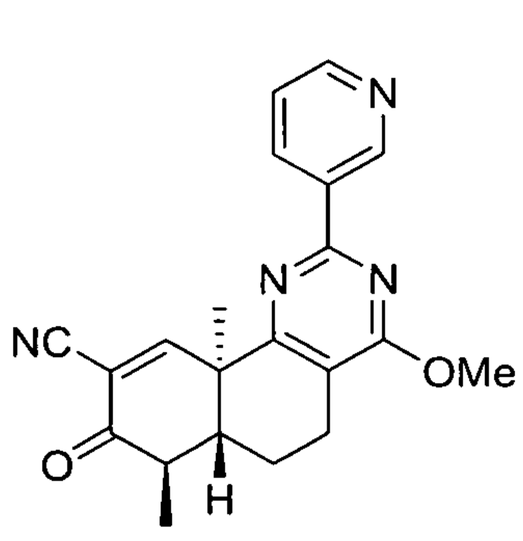
A_2 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$.

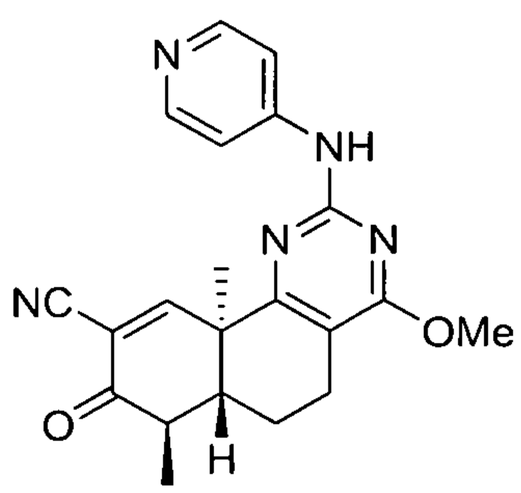
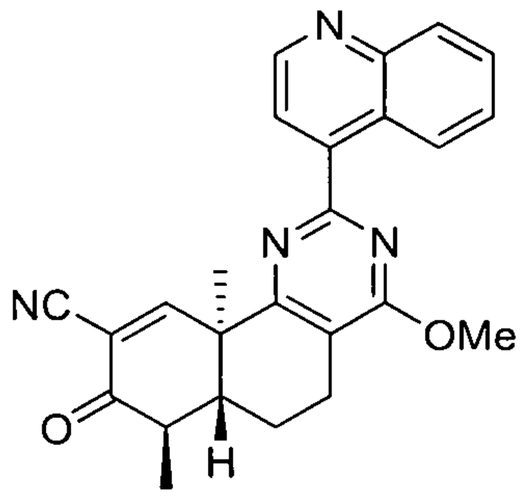
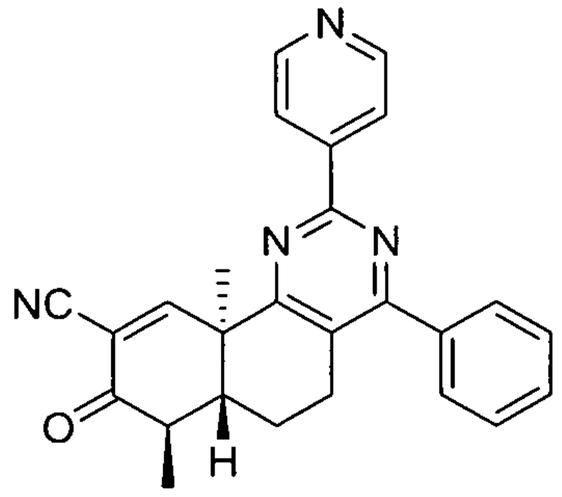
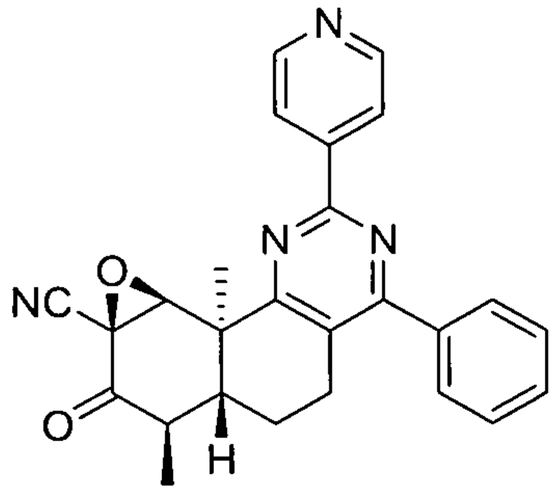
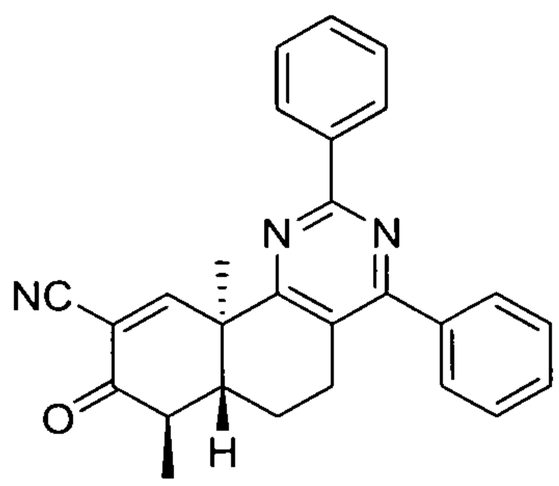
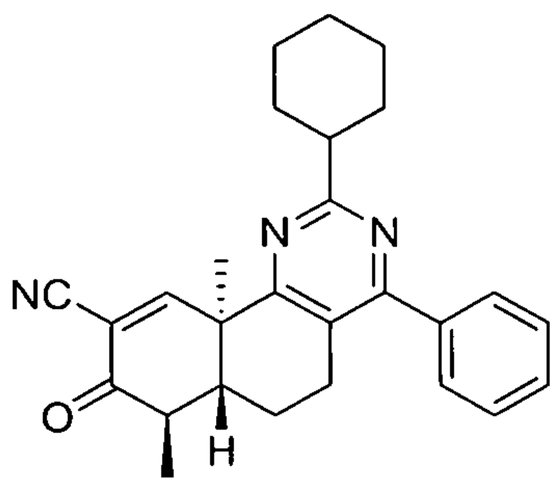
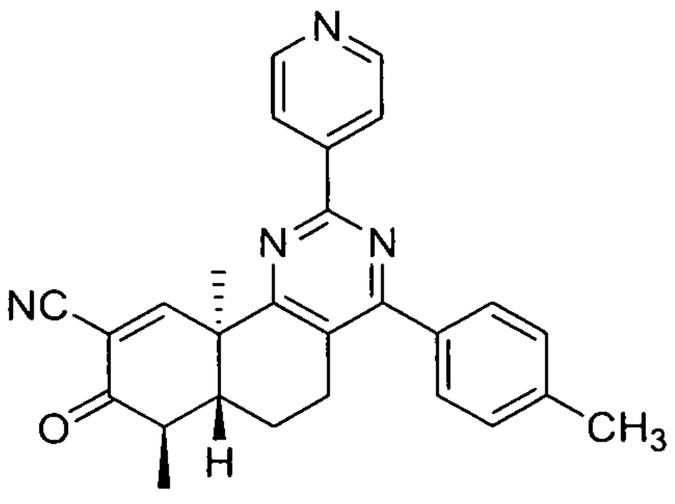
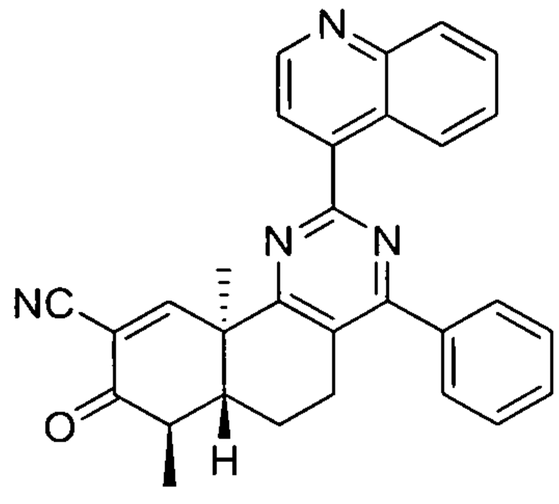
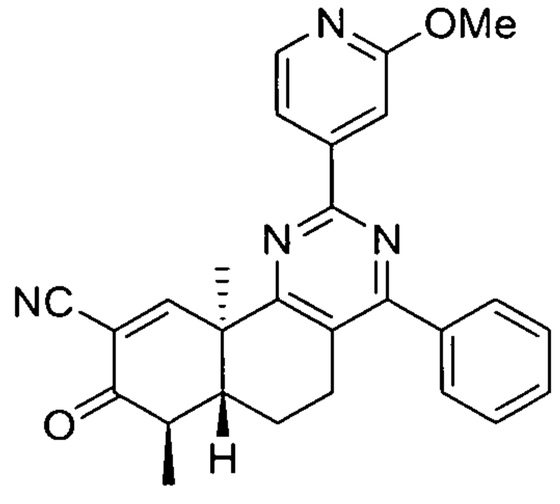
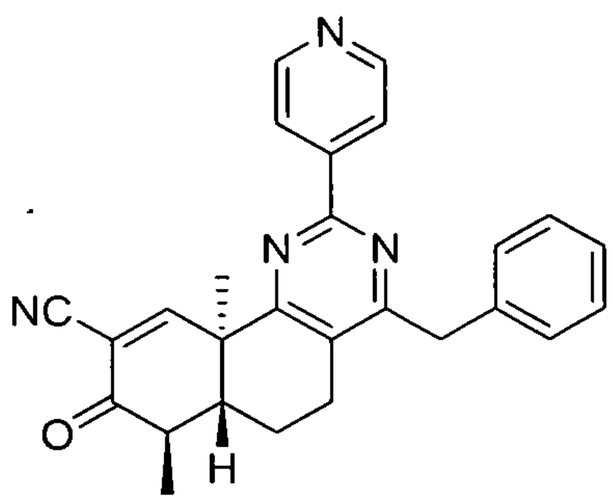
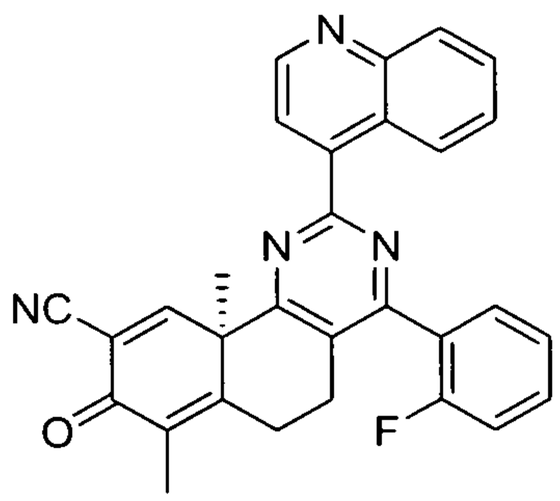
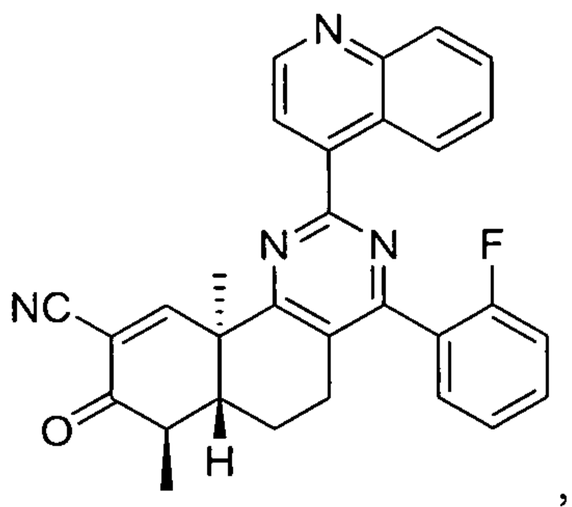
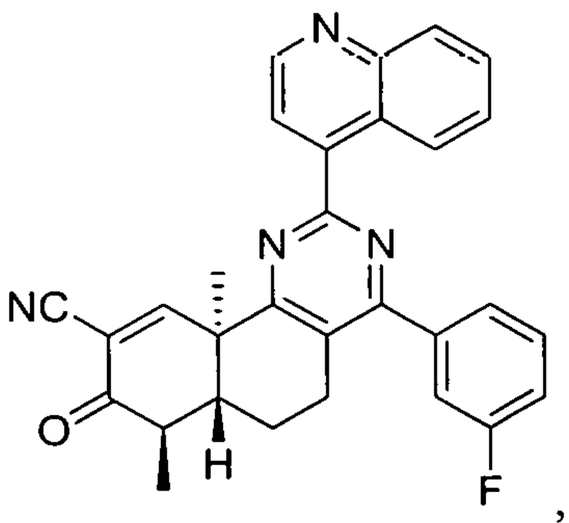
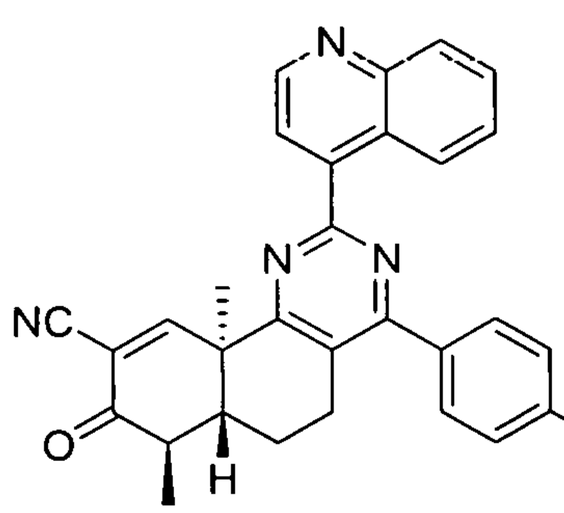
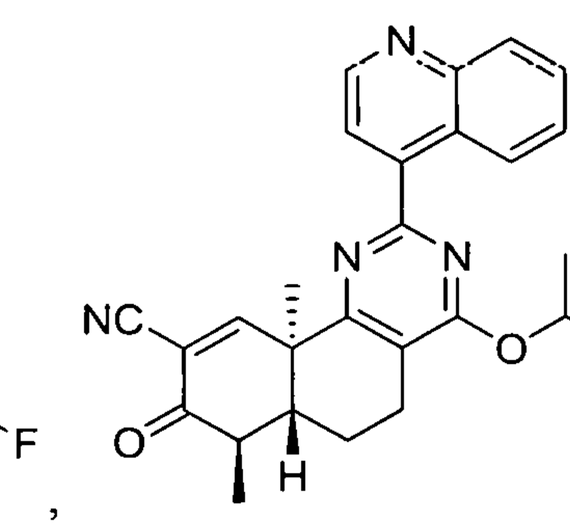
In some embodiments, Y_2 is arenediyl$_{(C\leq8)}$ such as benzenediyl. In some embodiments, R_c is alkyl$_{(C\leq6)}$ such as methyl. In some embodiments, A_2 is aralkyl$_{(C\leq12)}$ such as benzyl.

In other embodiments, R_5 is heteroaryl$_{(C\leq12)}$ or substituted heteroaryl$_{(C\leq12)}$. In some embodiments, R_5 is heteroaryl$_{(C\leq12)}$ such as 5-(3-methyl)-oxadiazolyl, 4-(3,5-dimethyl)-isoxazolyl, furanyl, benzofuranyl, 2-thiazolyl, 5-(2-methyl)-furanyl, 3-pyridinyl, or 4-pyridinyl. In other embodiments, R_5 is hydroxy. In other embodiments, R_5 is $-OS(O)_2C_6H_4CH_3$. In other embodiments, R_5 is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12)}$. In some embodiments, R_5 is heterocycloalkyl$_{(C\leq12)}$ such as pyrrolidinyl. In other embodiments, R_5 is alkoxy$_{(C\leq12)}$ or substituted alkoxy$_{(C\leq12)}$. In some embodiments, R_5 is alkoxy$_{(C\leq12)}$ such as methoxy or isopropoxy. In other embodiments, R_5 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$. In some embodiments, R_5 is aralkyl$_{(C\leq12)}$ such as benzyl.

In some embodiments, the compounds are further defined as:


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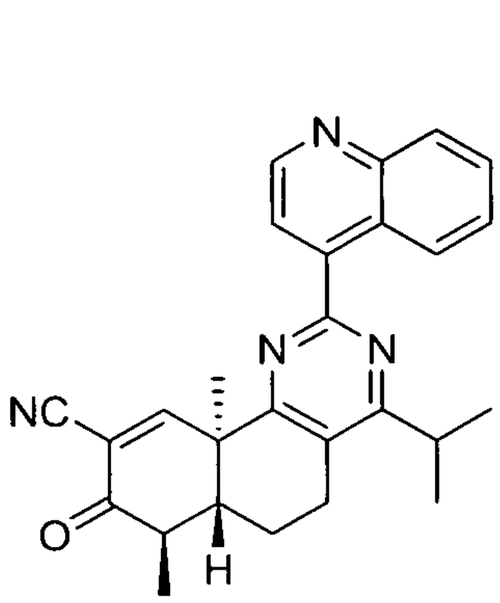
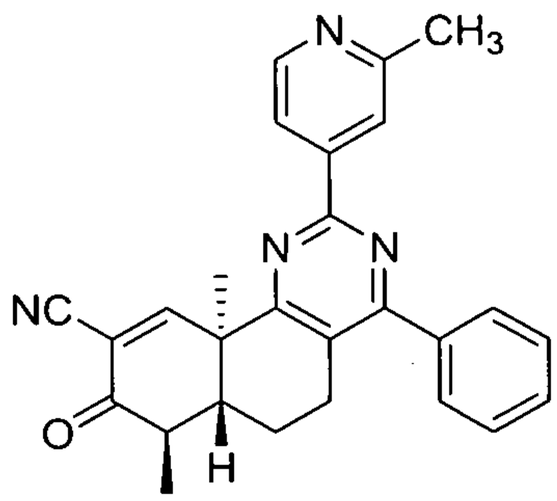
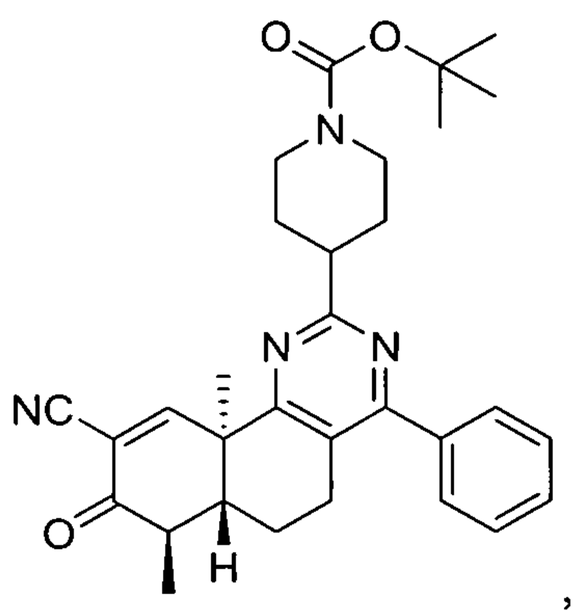

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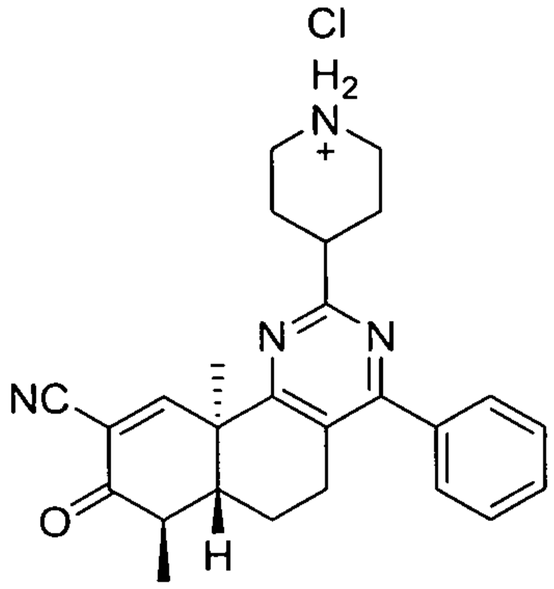
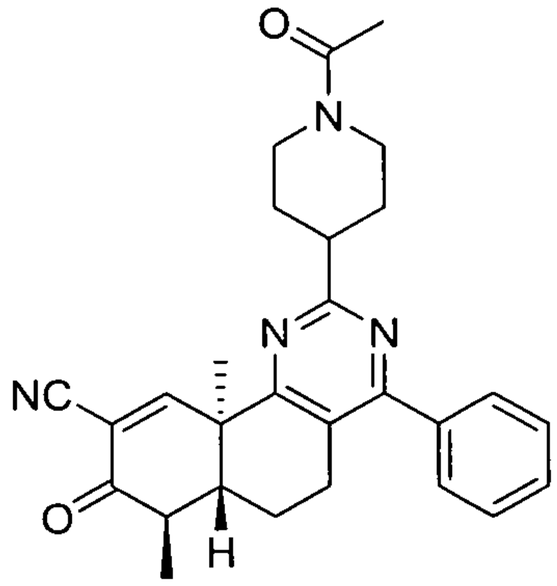
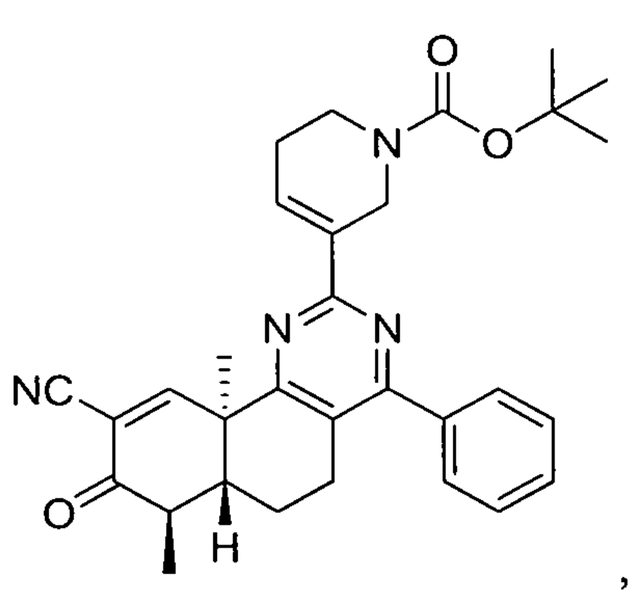
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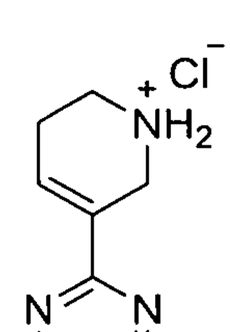
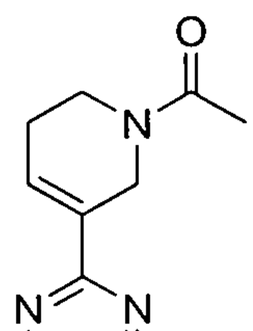
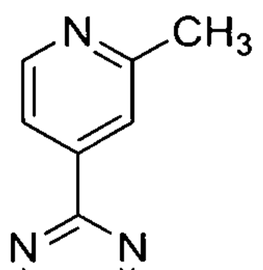
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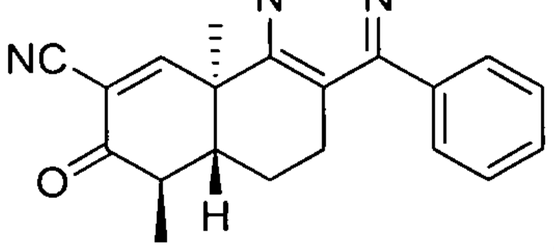
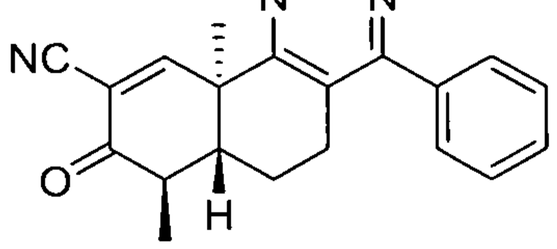
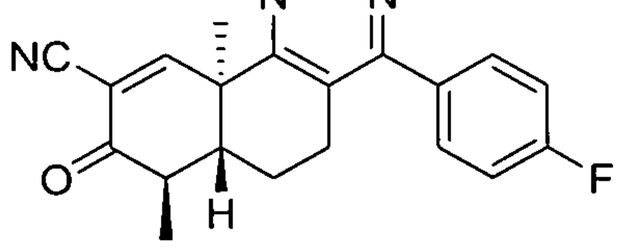
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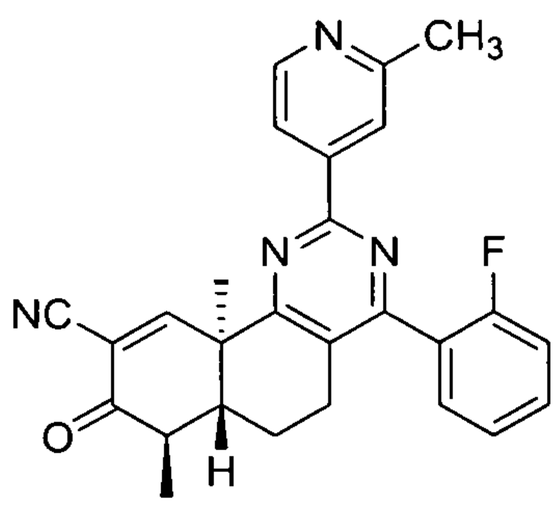
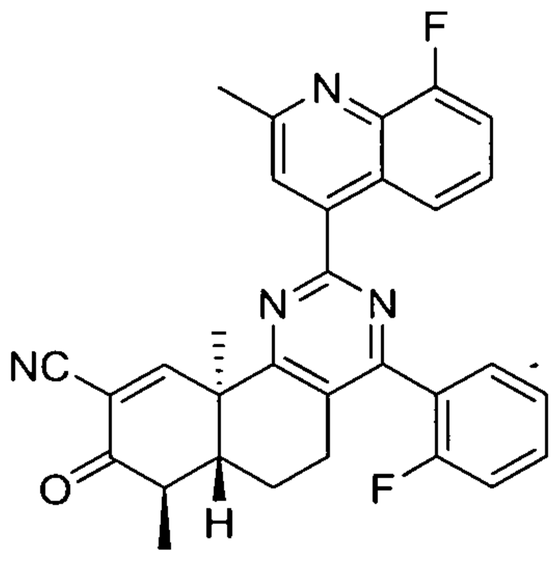
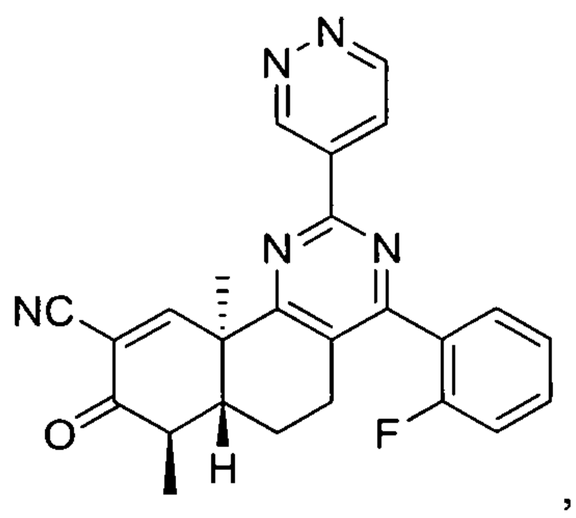

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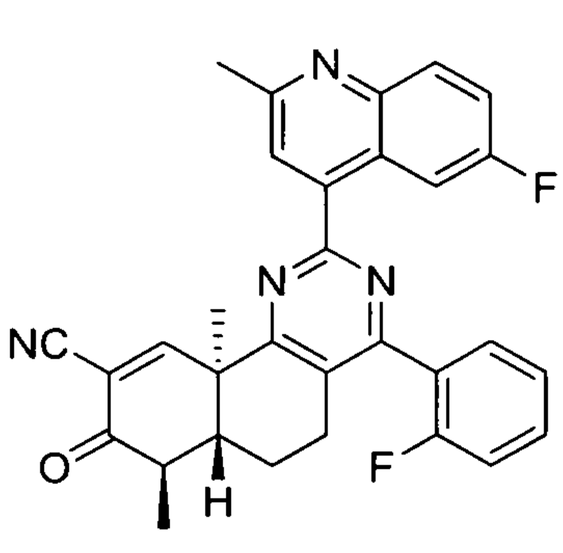
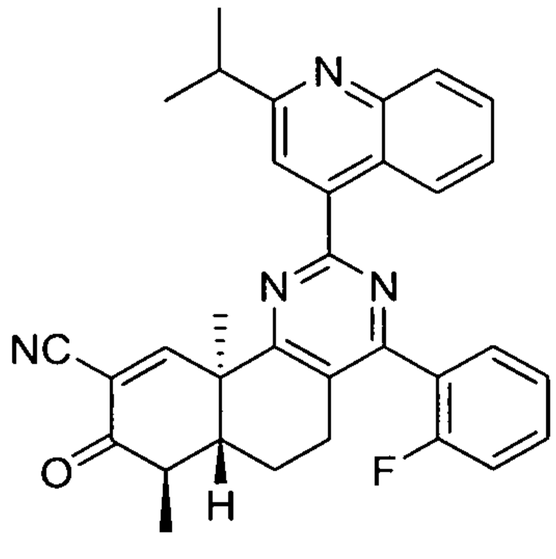
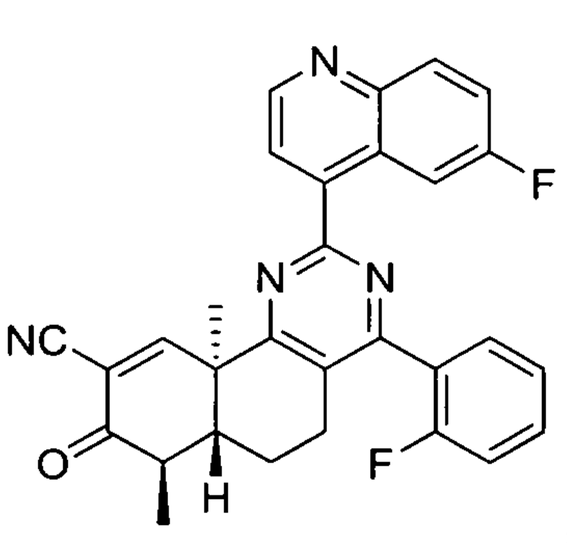
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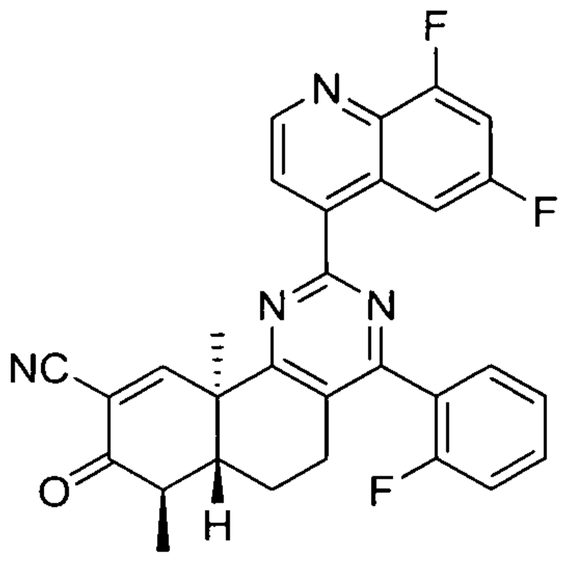
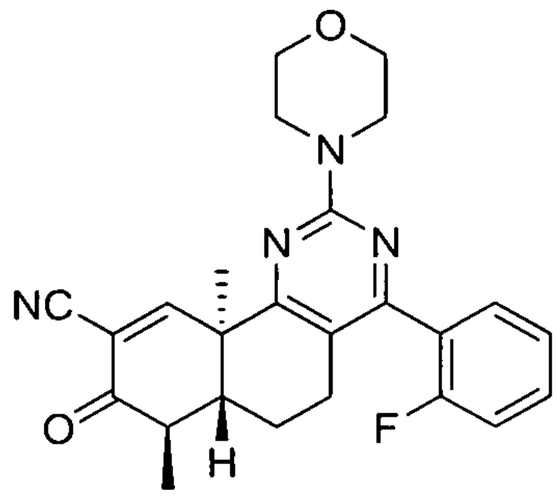
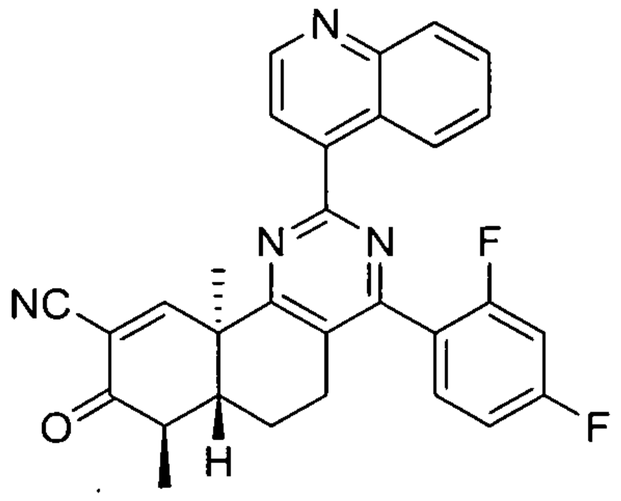
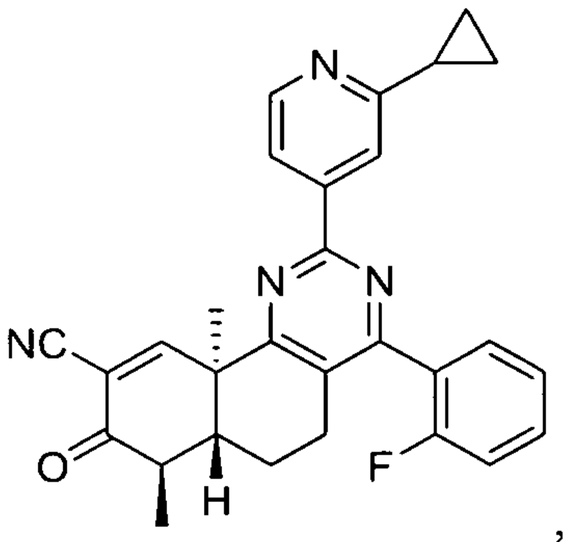
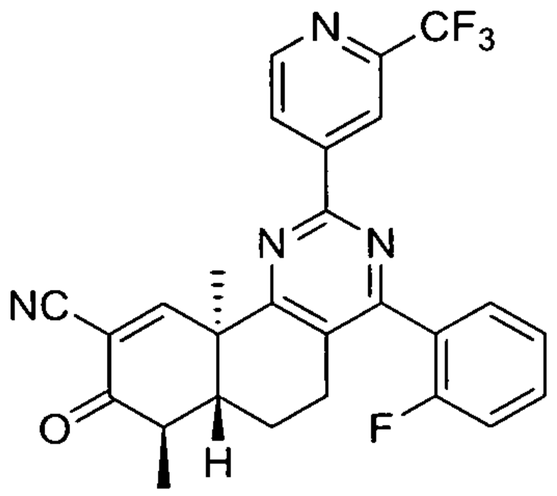
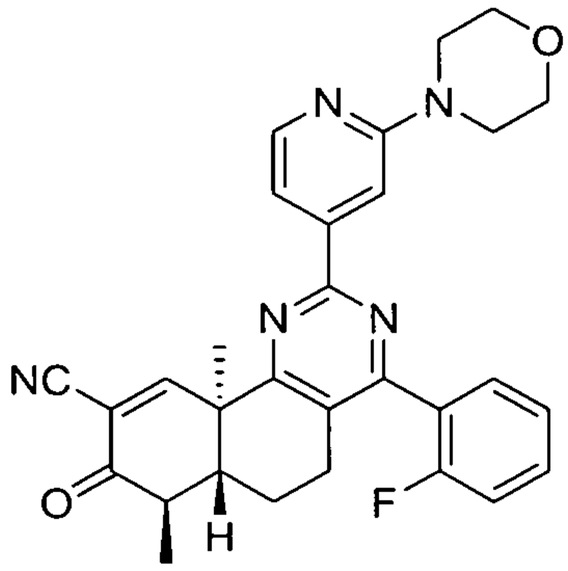
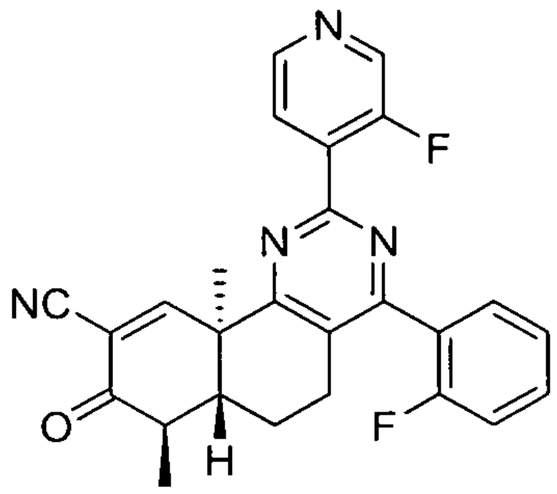
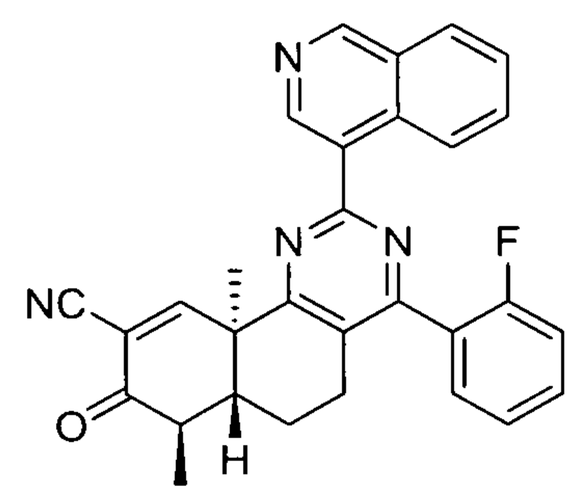
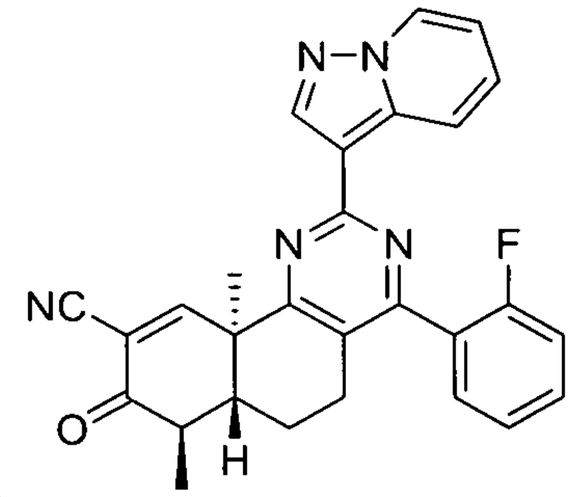
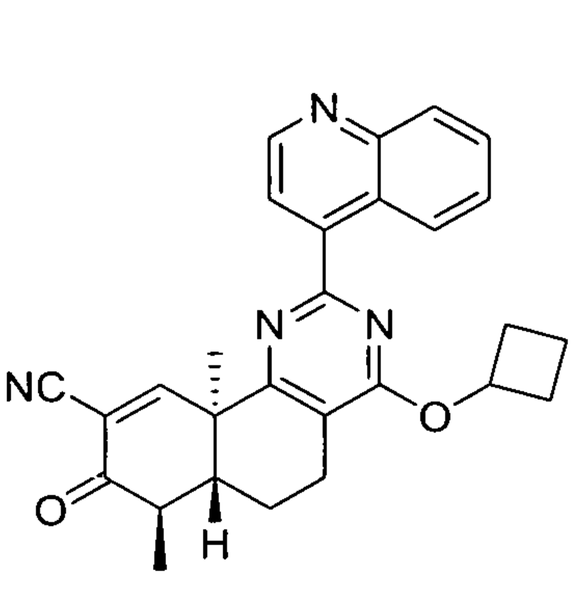
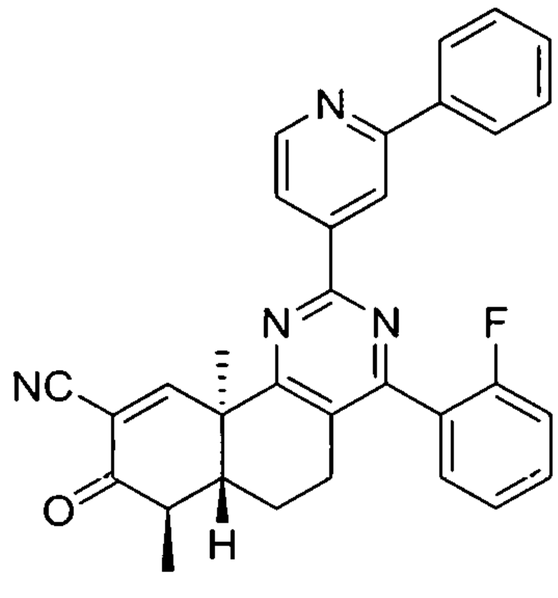
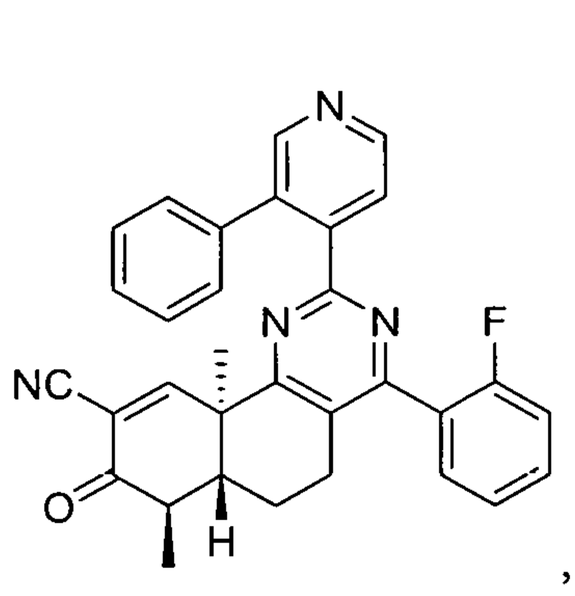
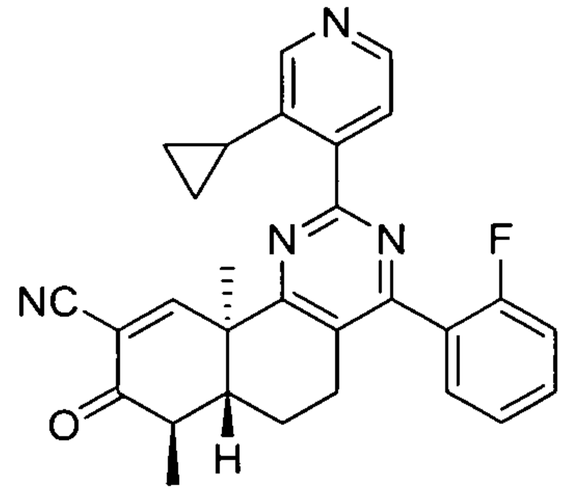
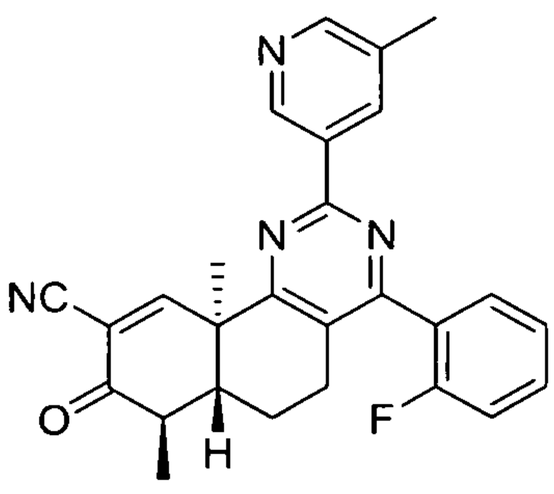
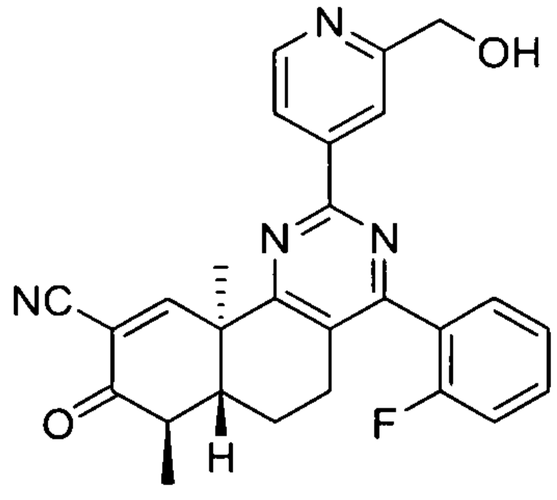




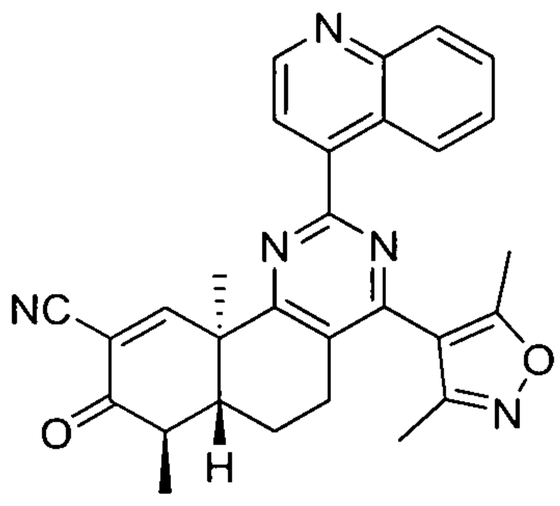
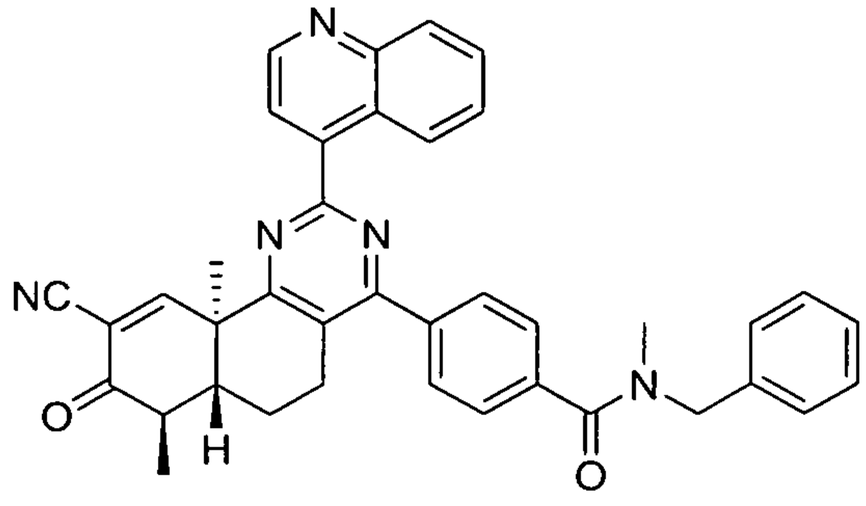
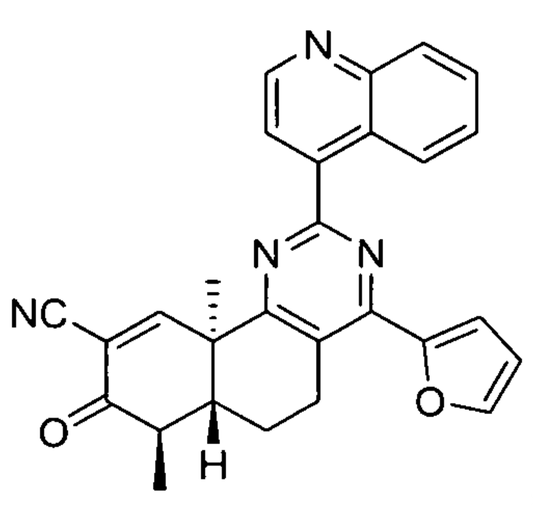
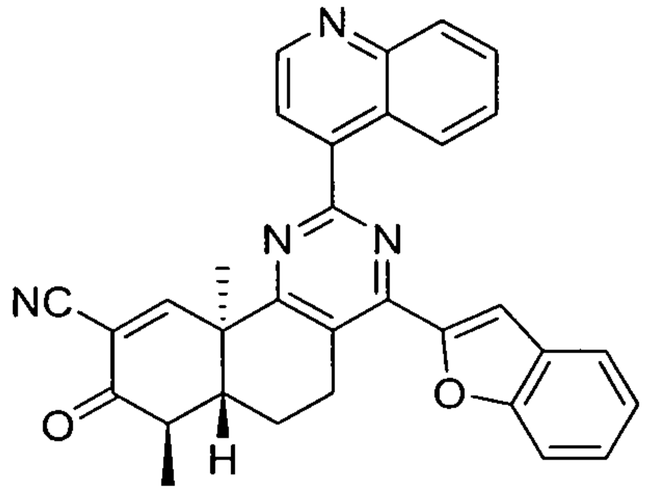
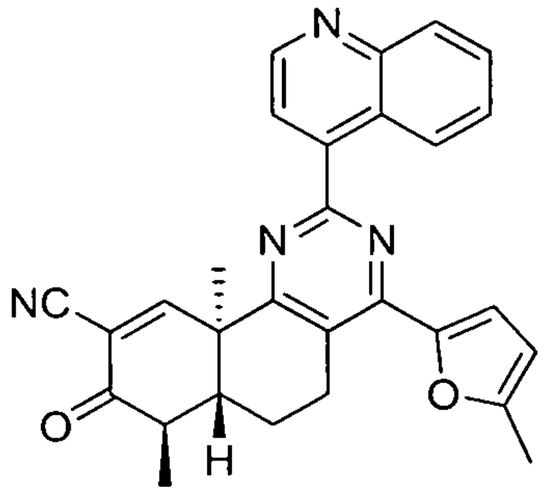
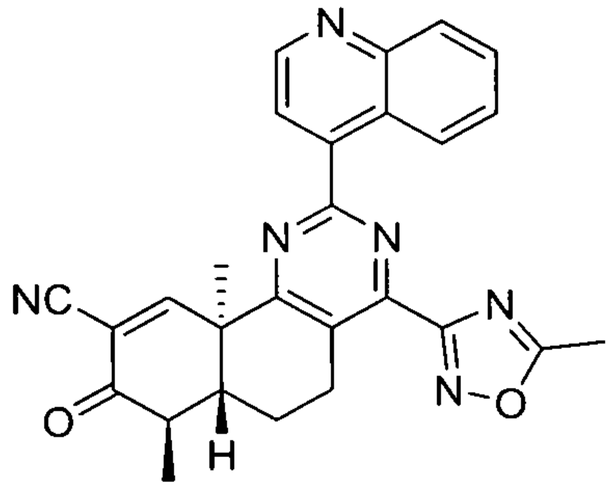
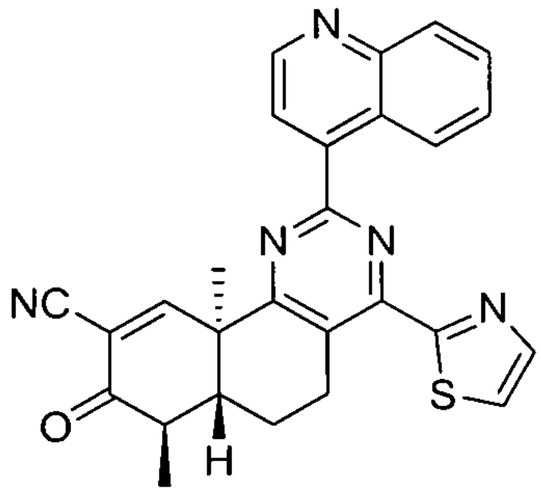
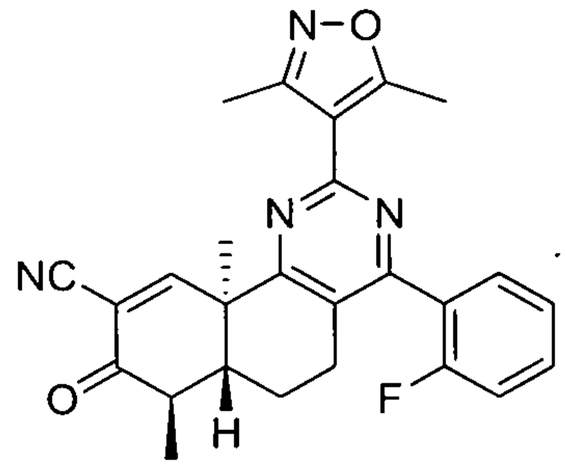
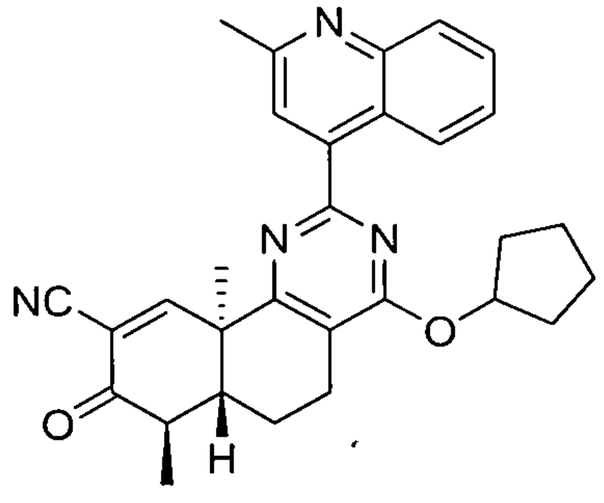
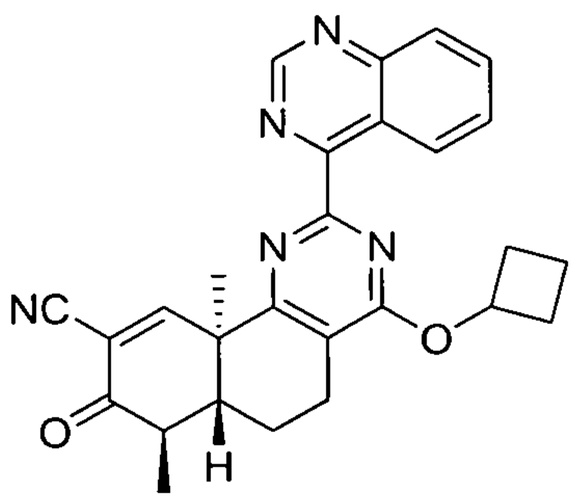
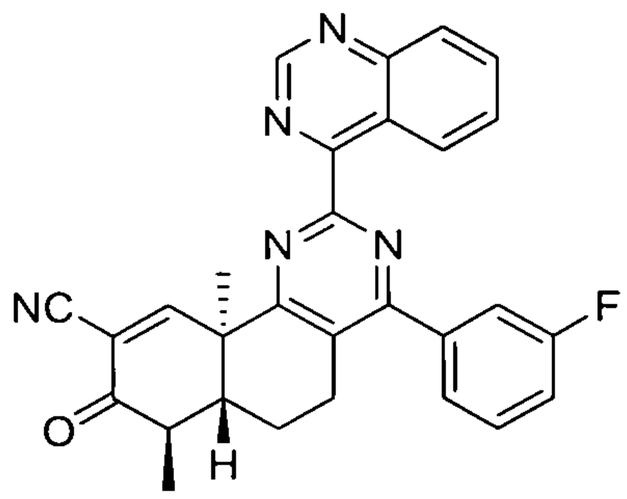
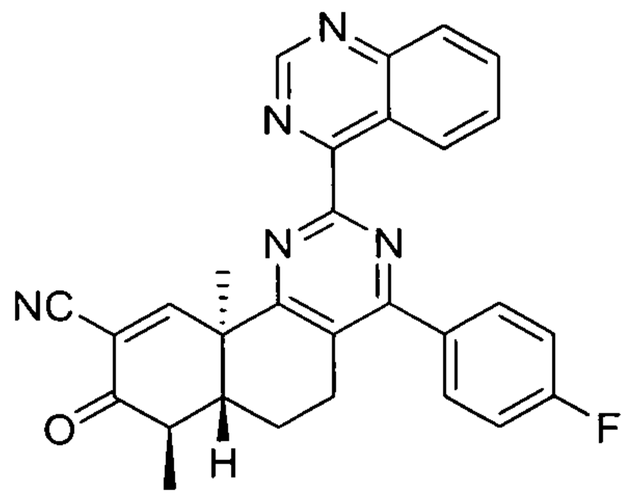
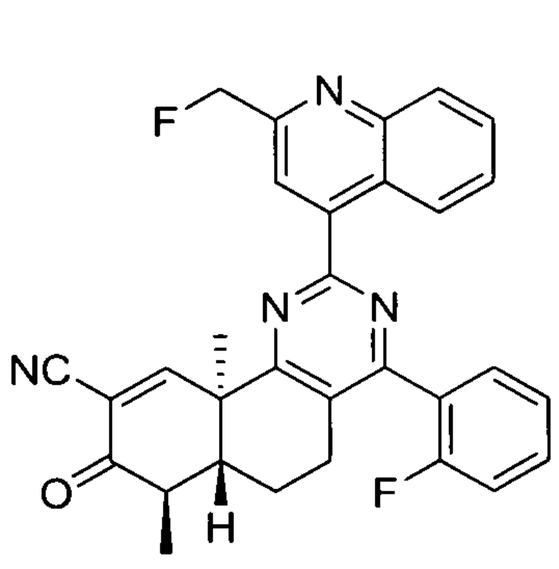
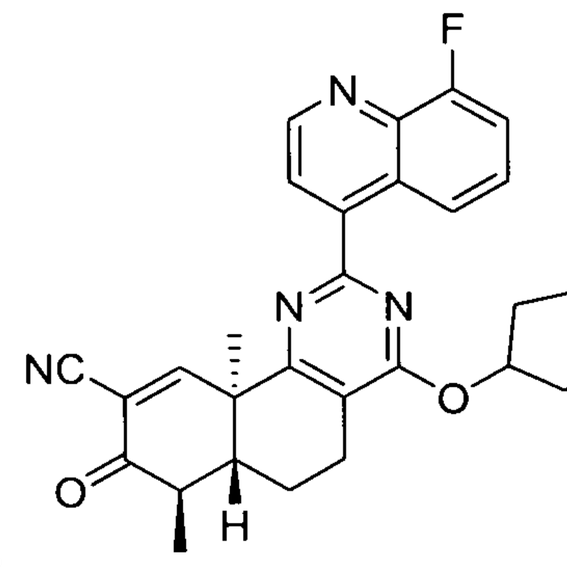
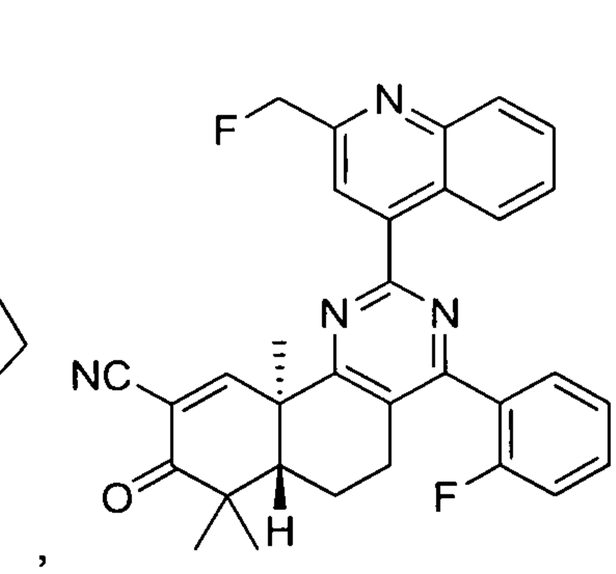

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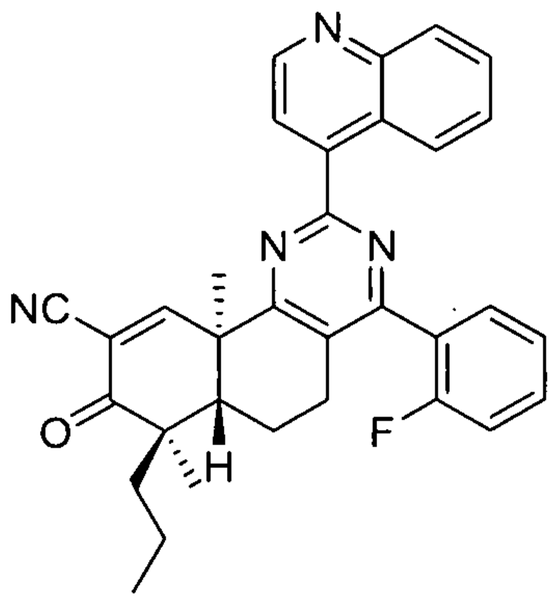
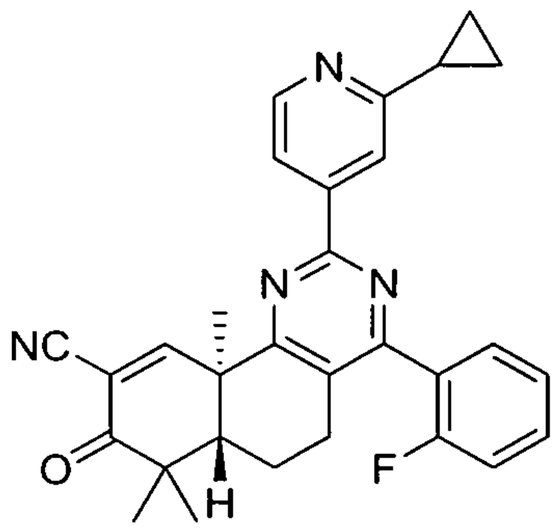
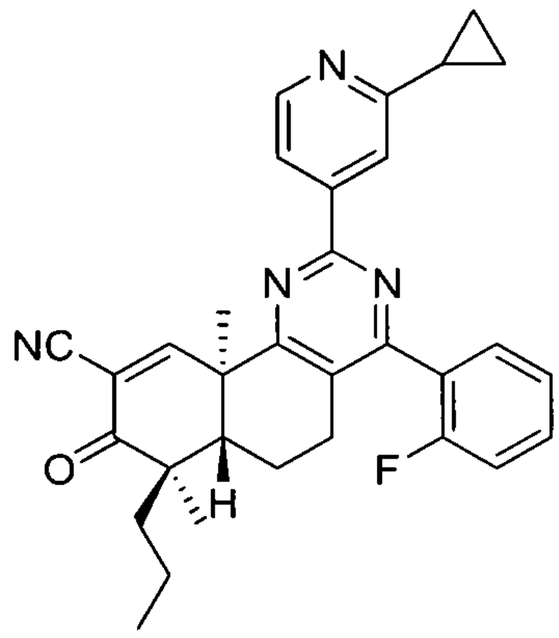
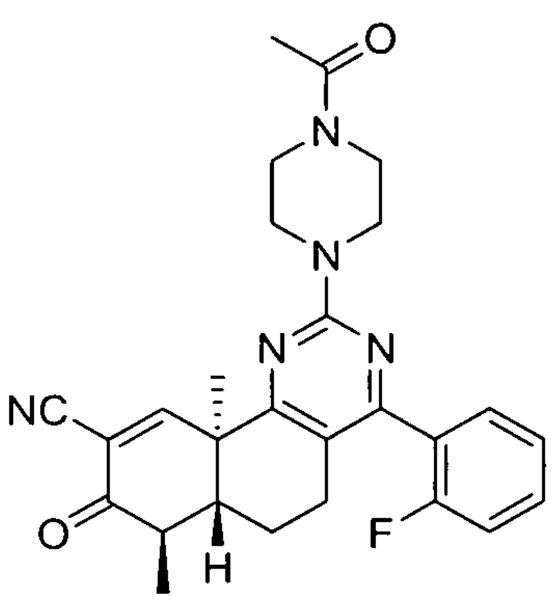
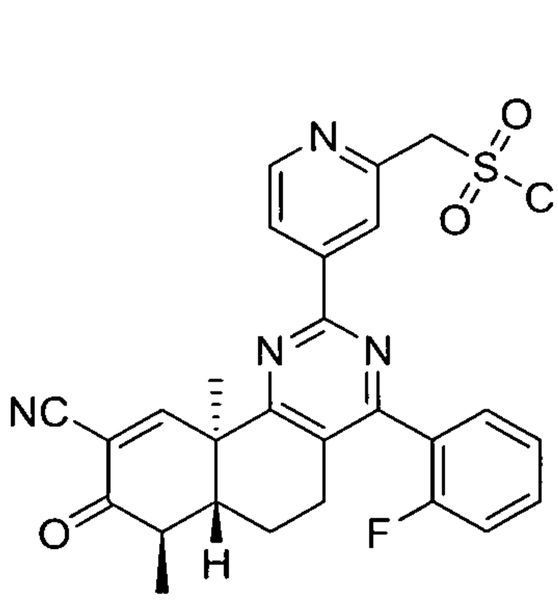
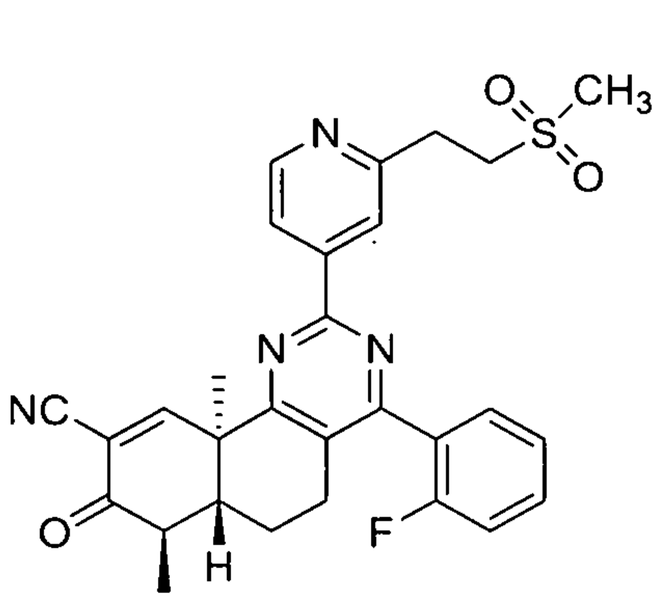
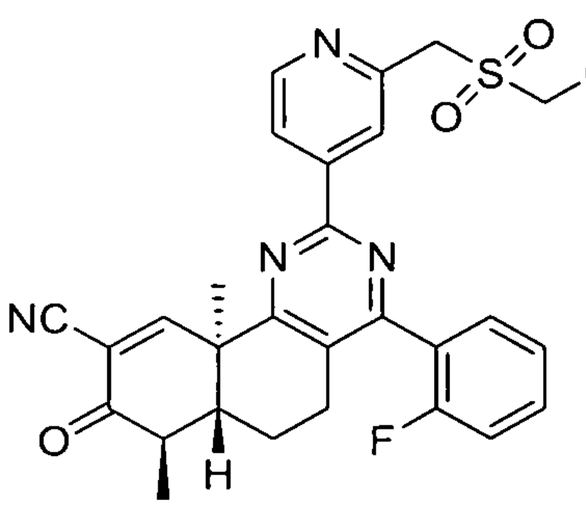
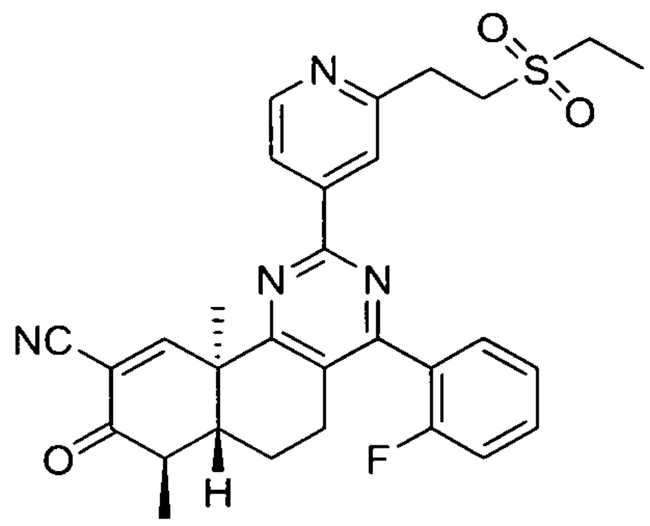
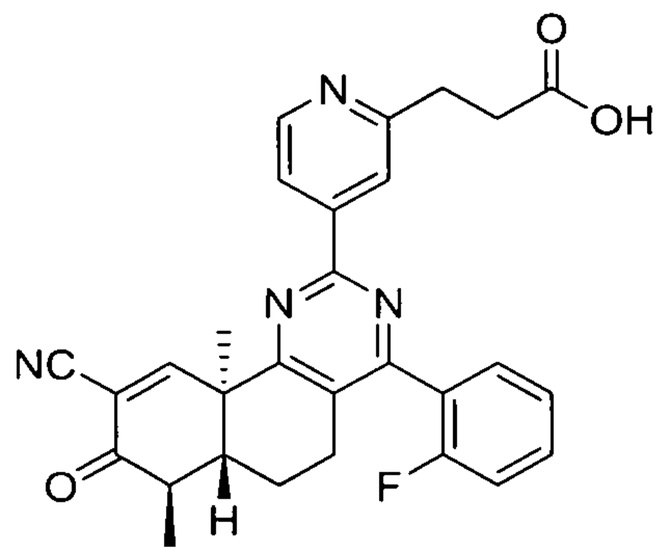
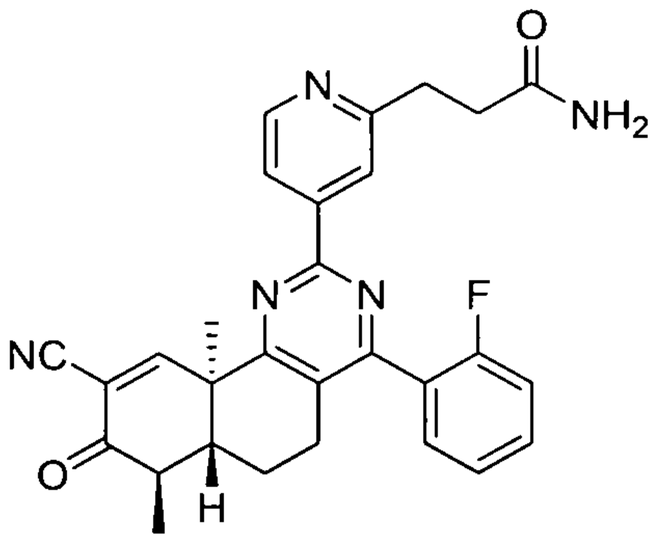
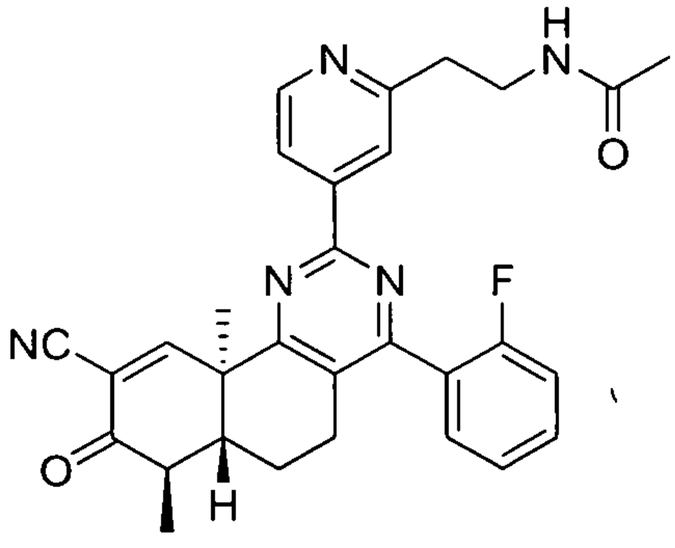
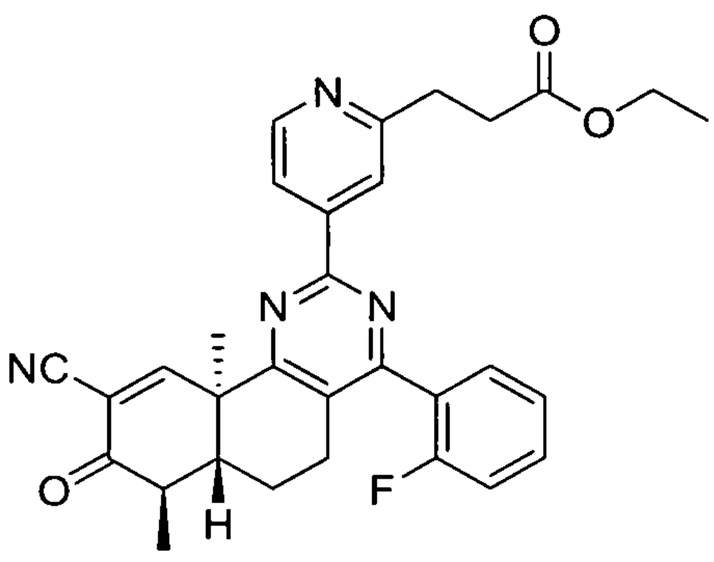
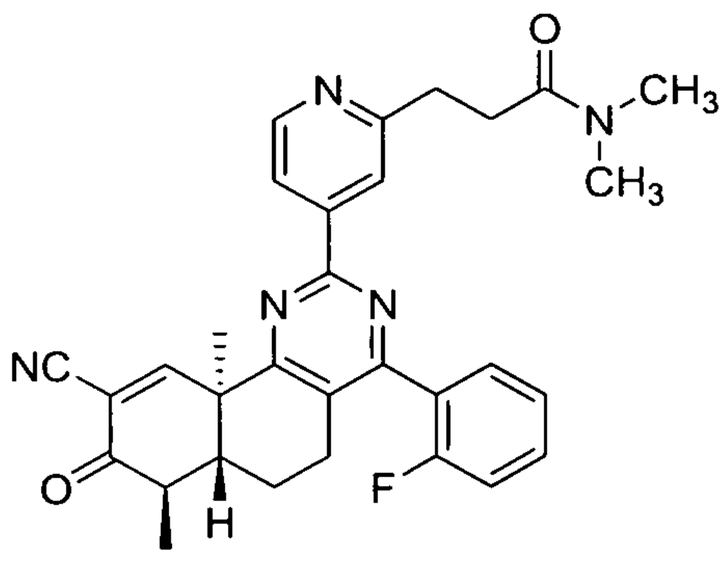
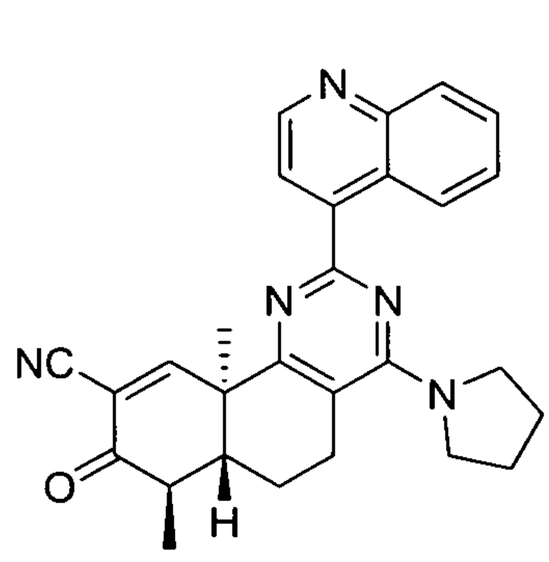
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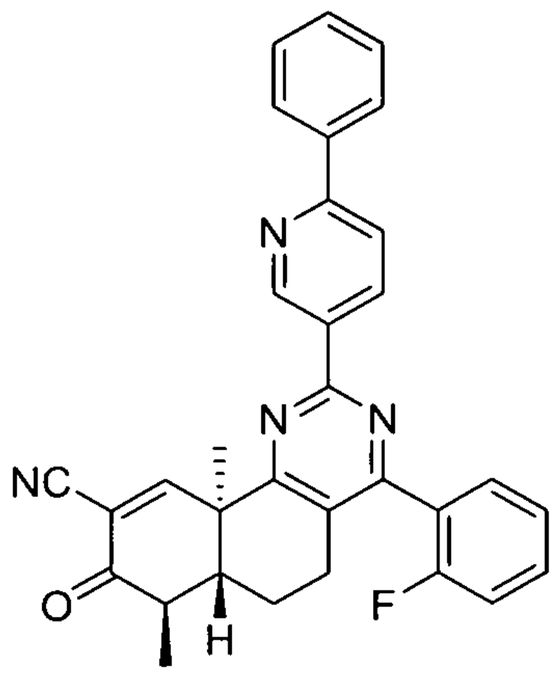
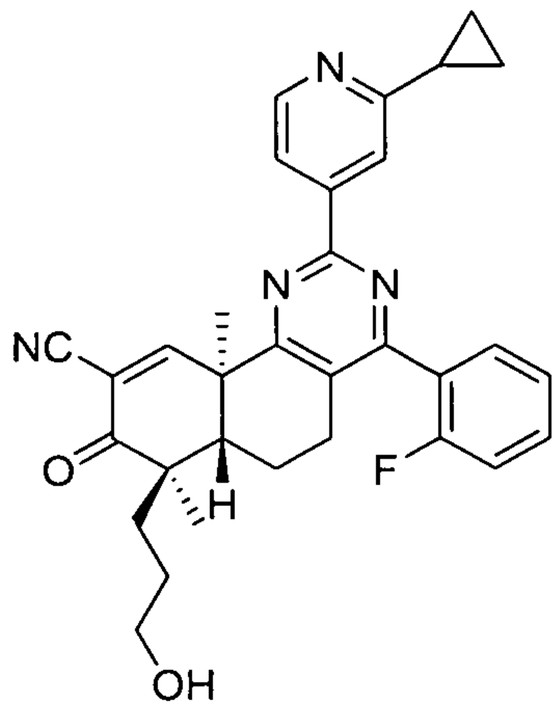
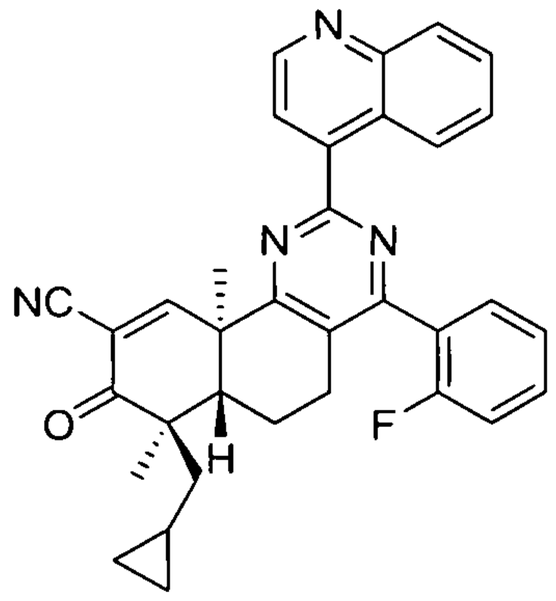
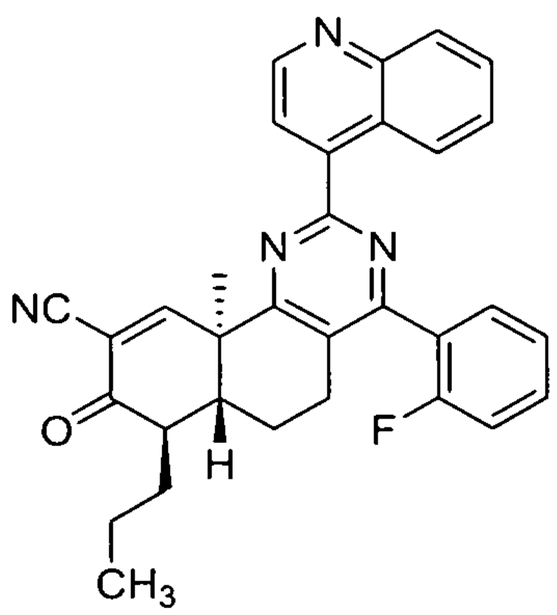
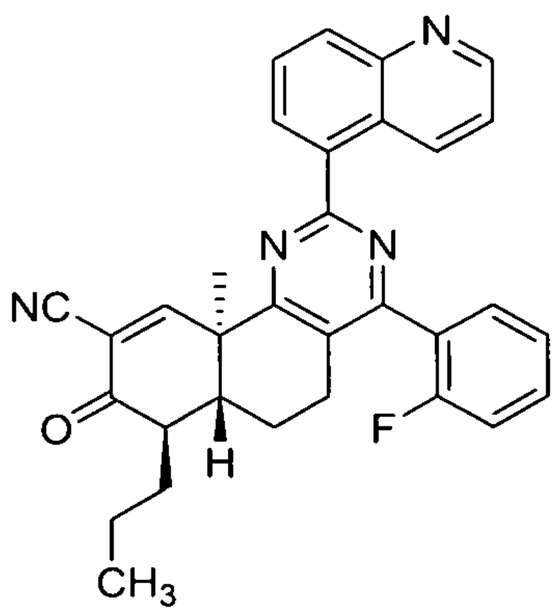
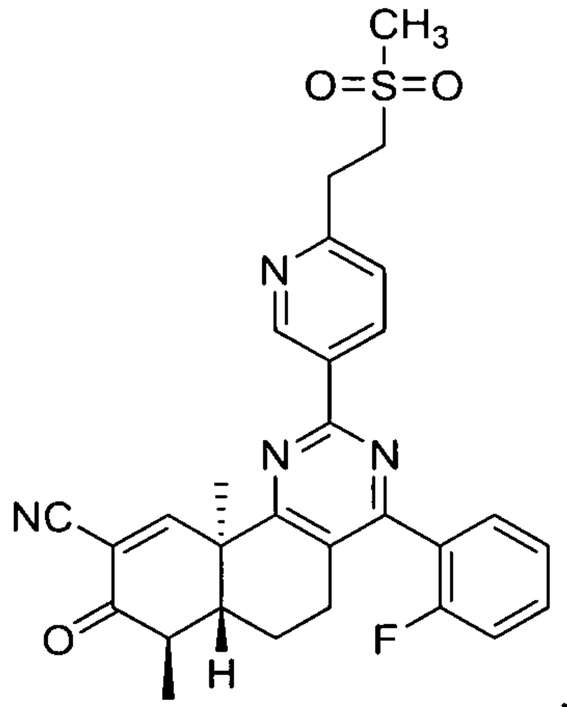
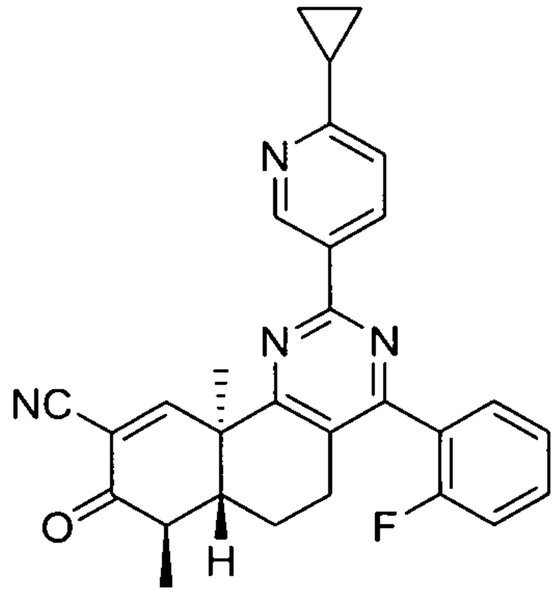
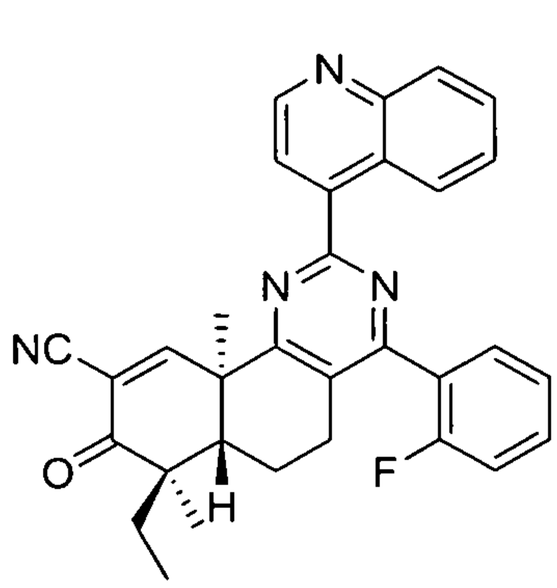
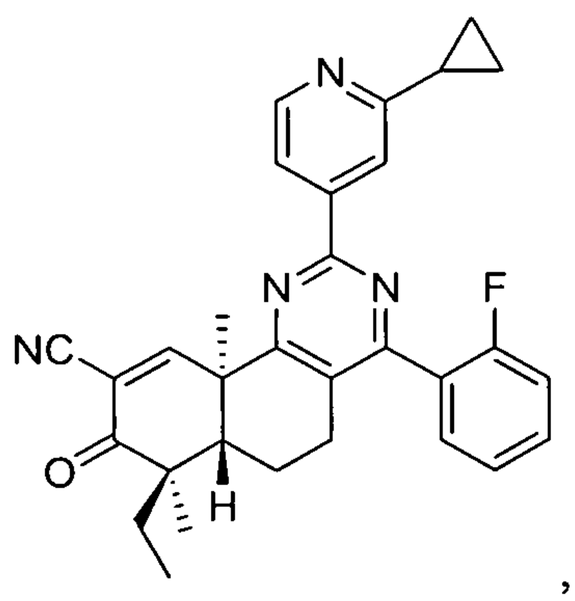
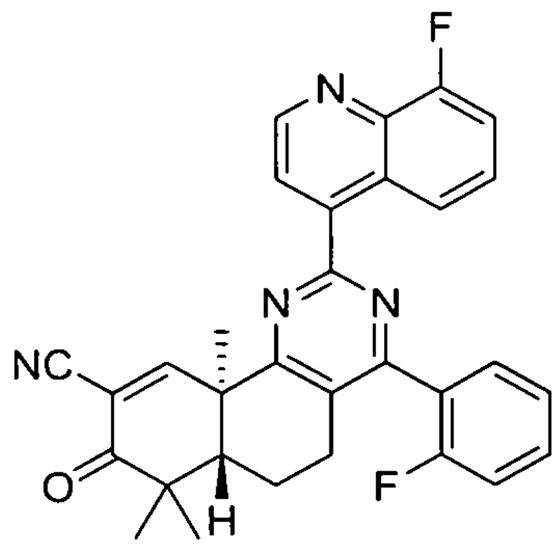
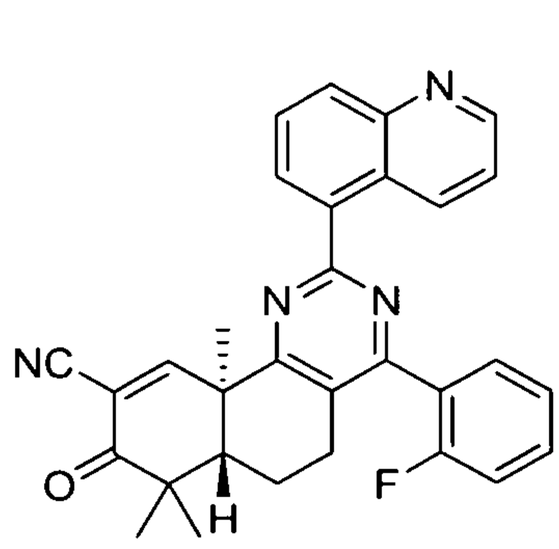
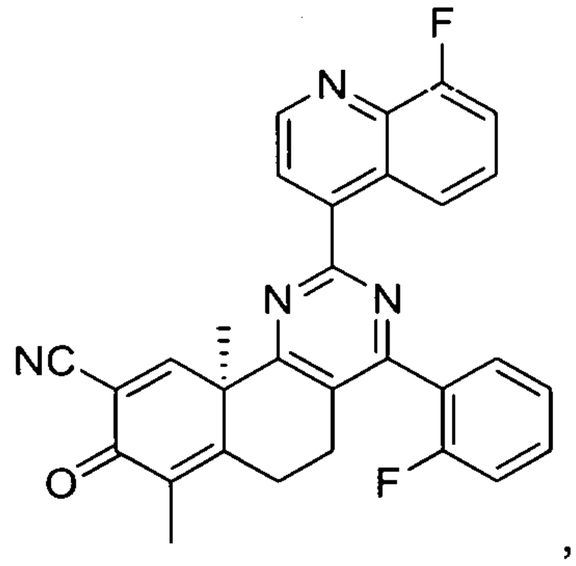

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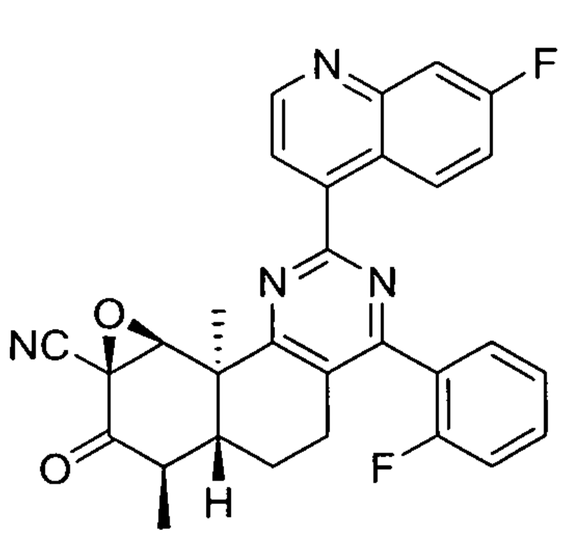
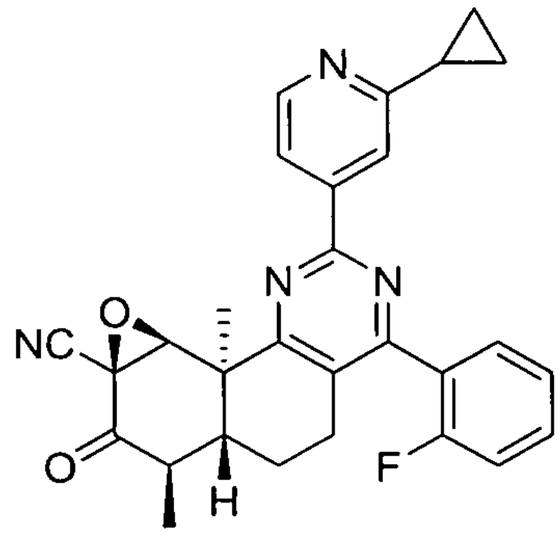
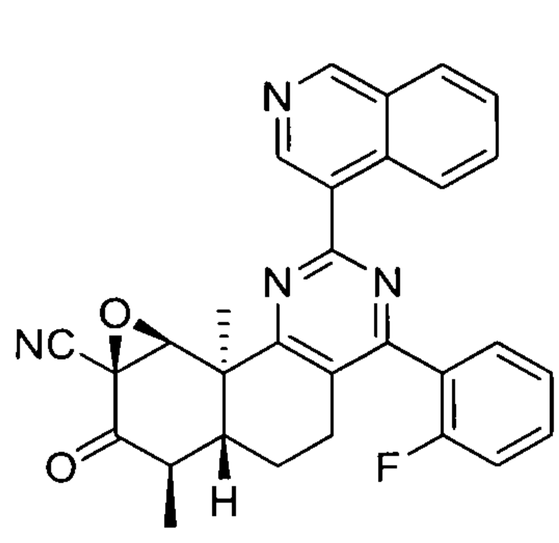
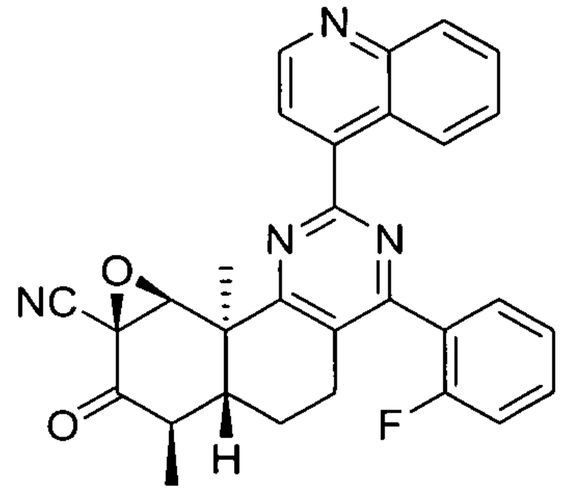
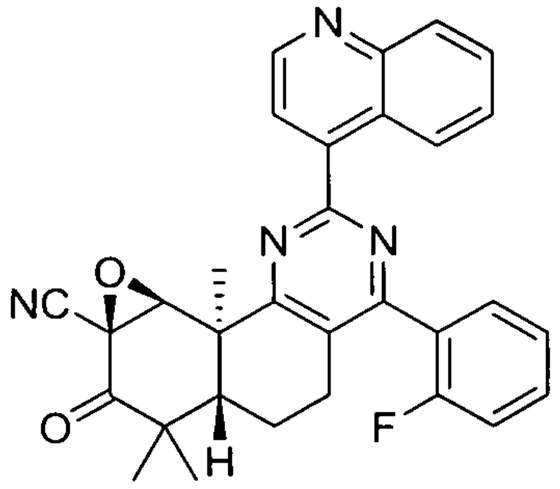
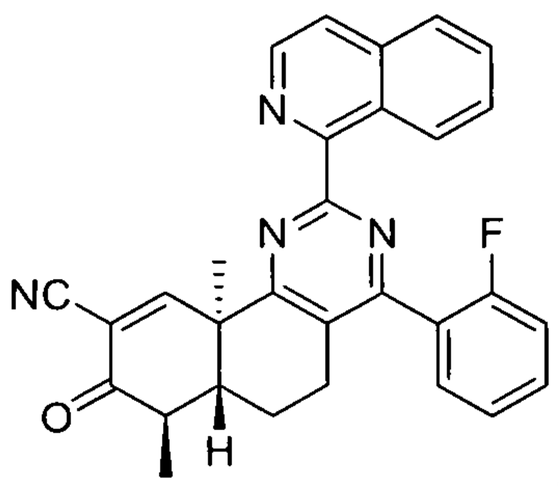
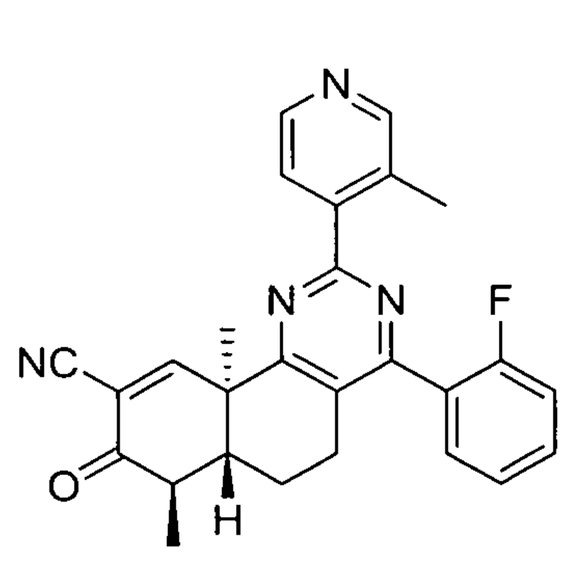
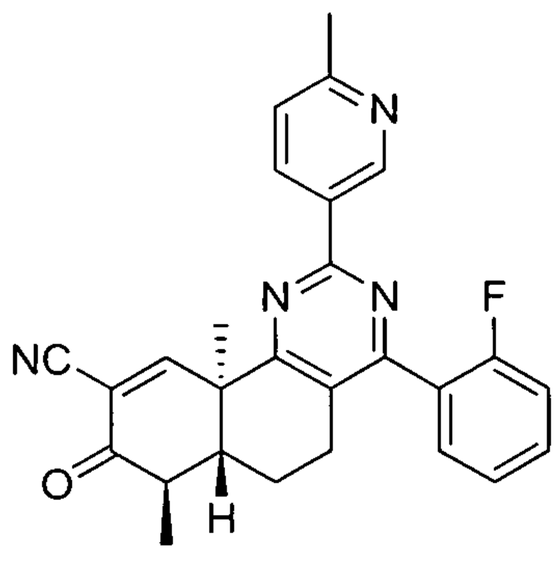
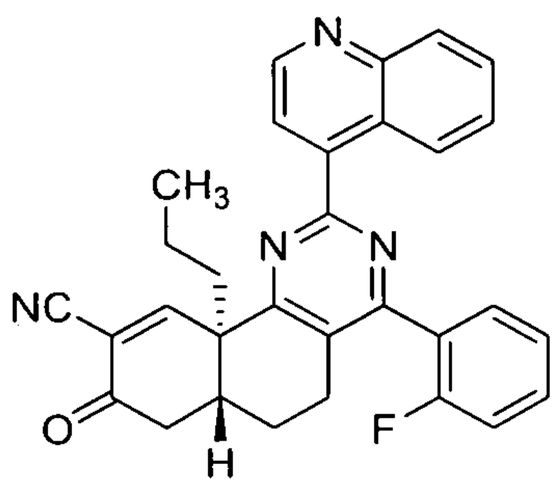
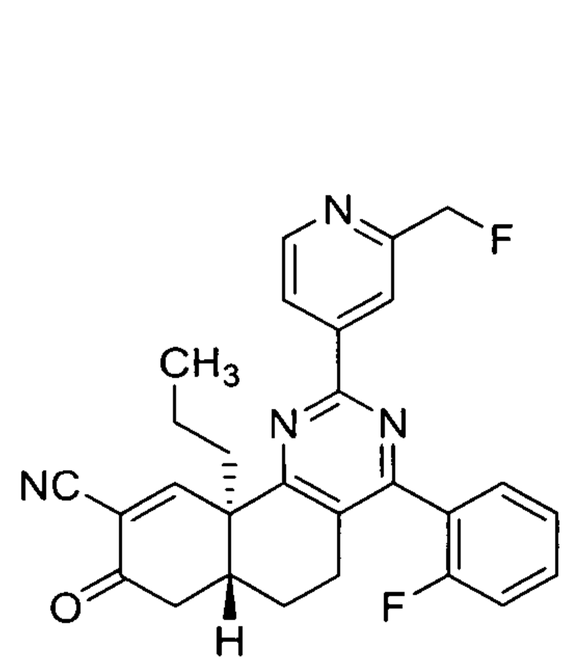
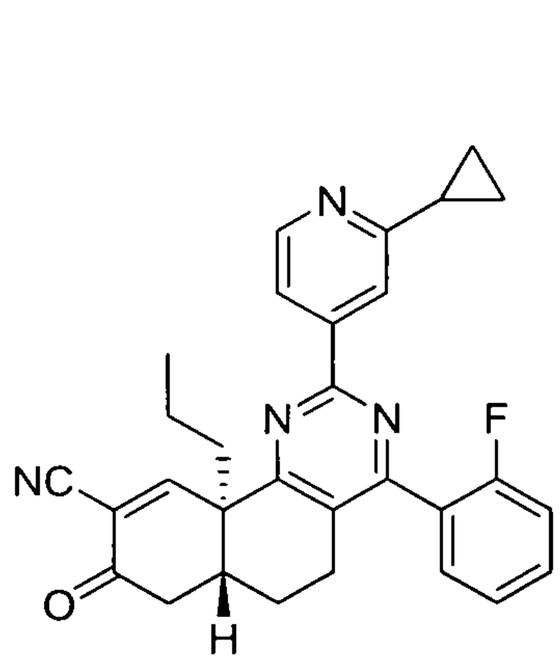
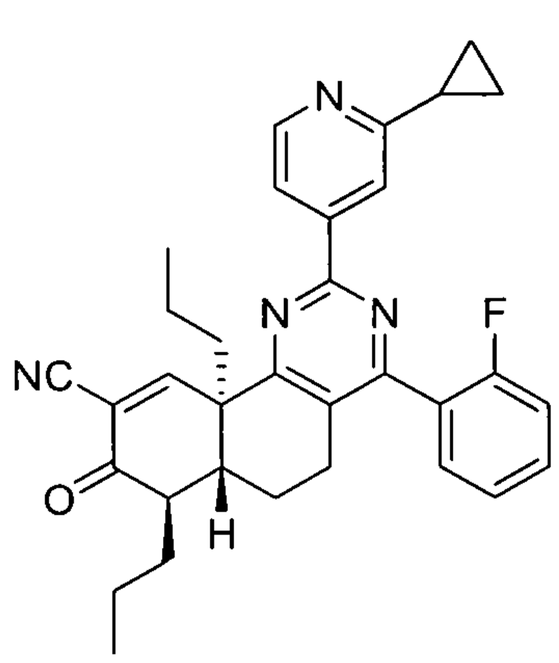
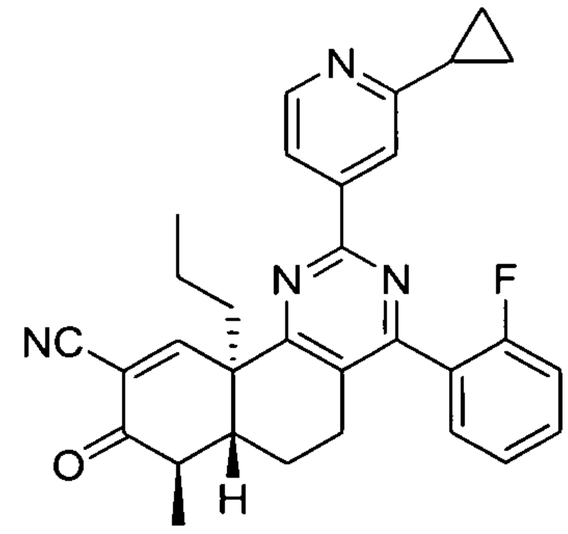
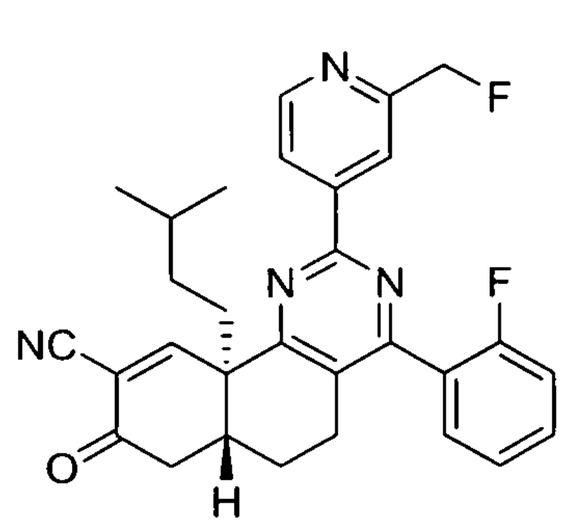
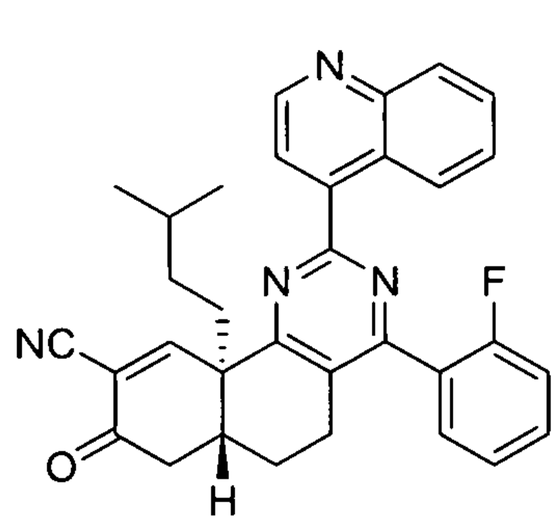

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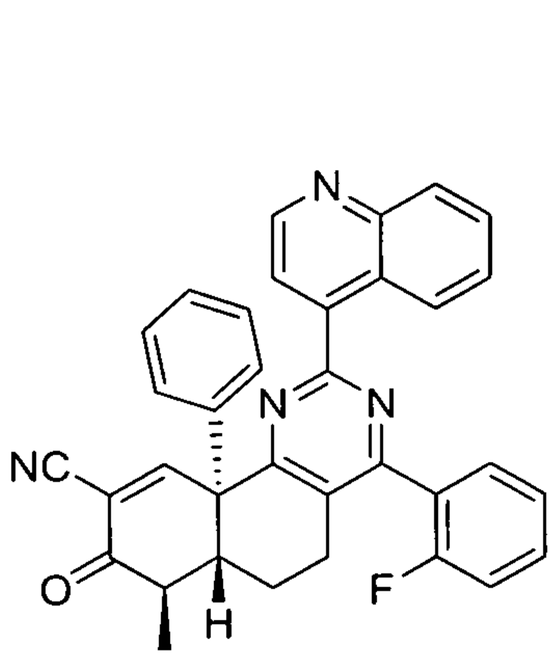
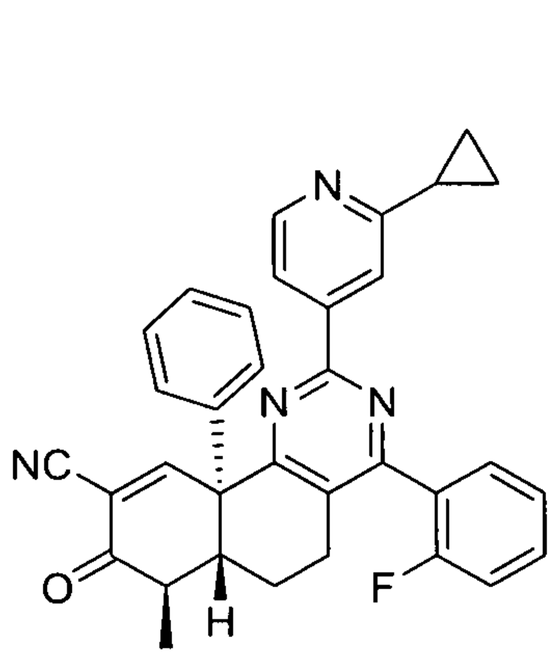
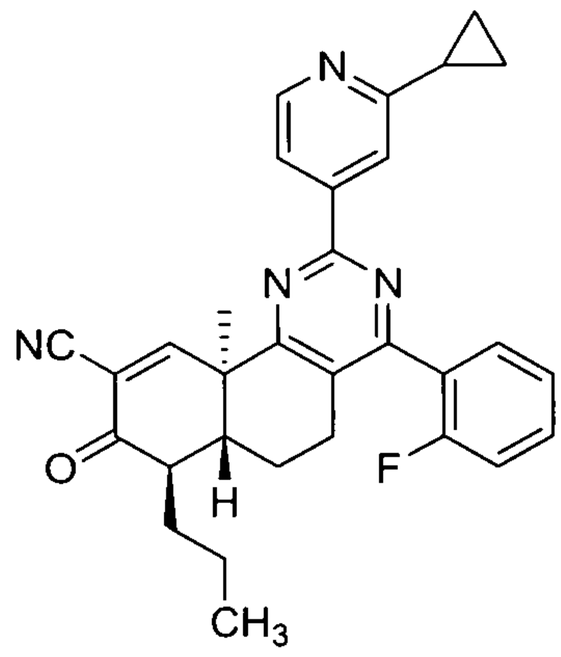
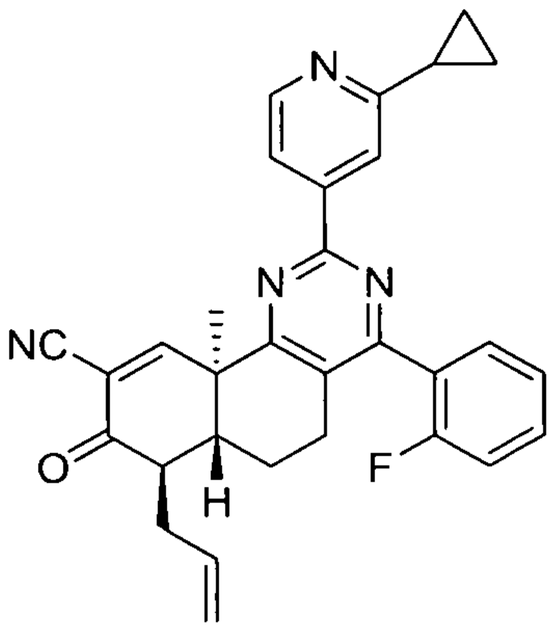
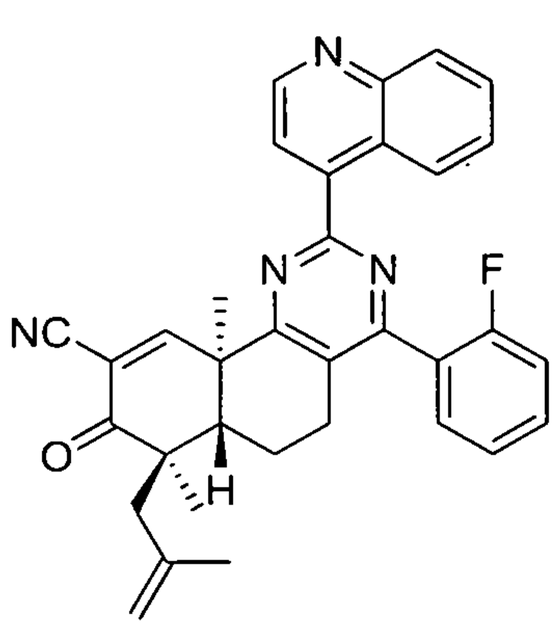
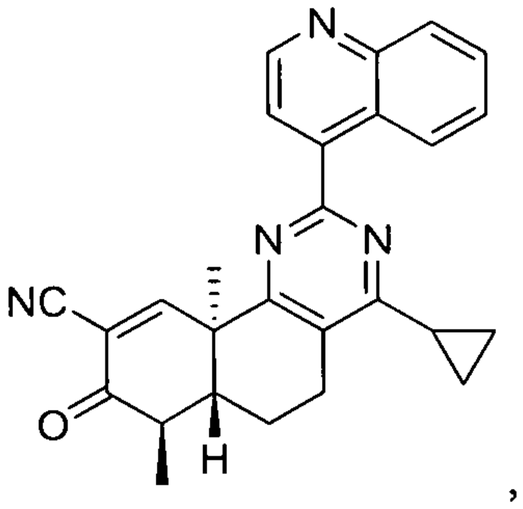
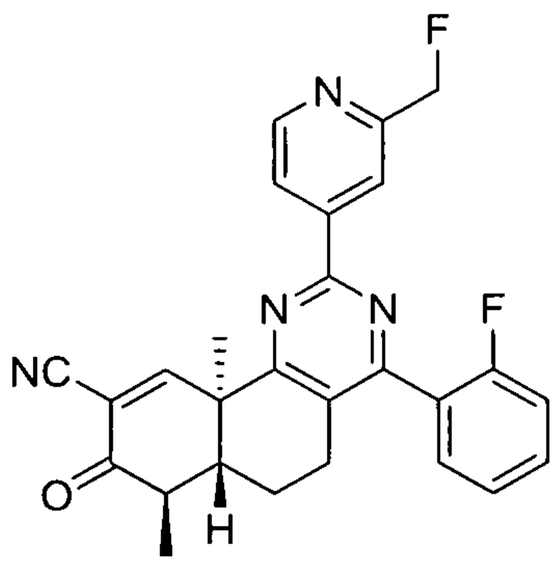
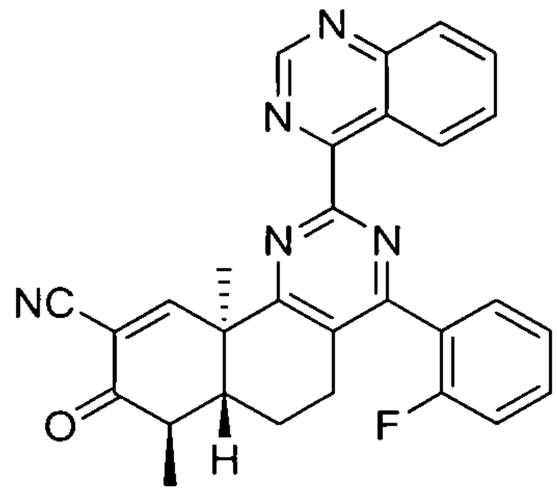
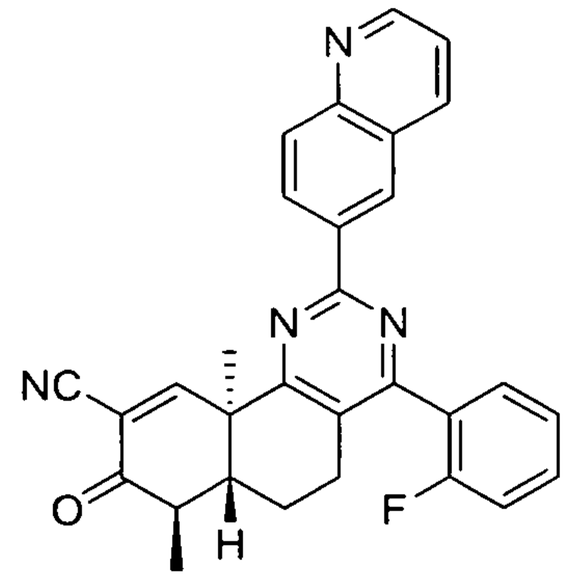
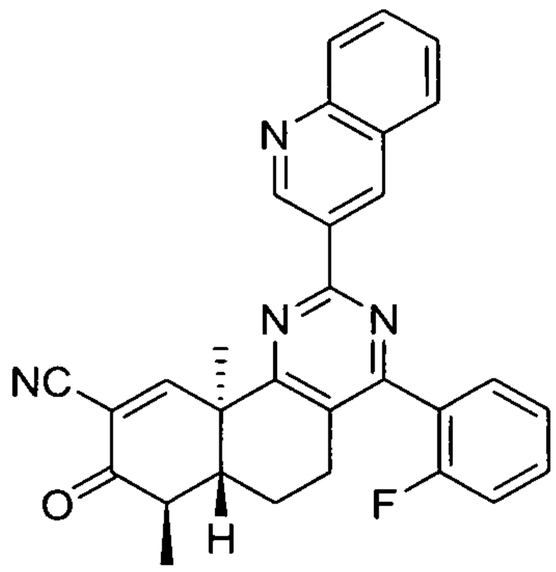
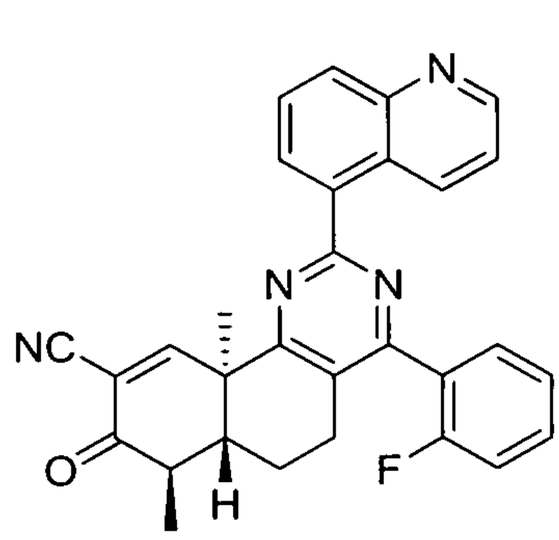
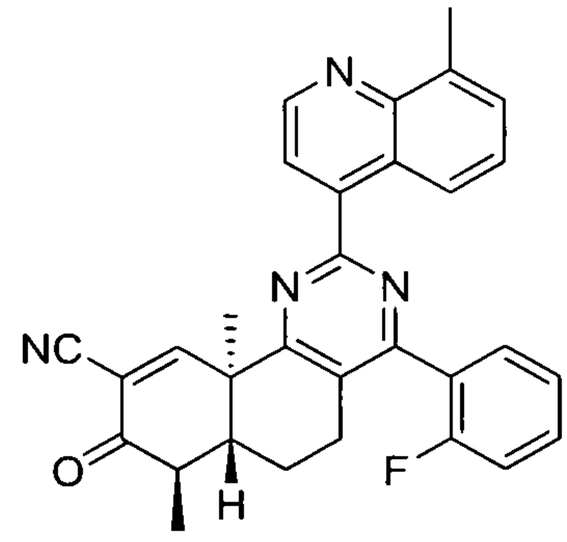
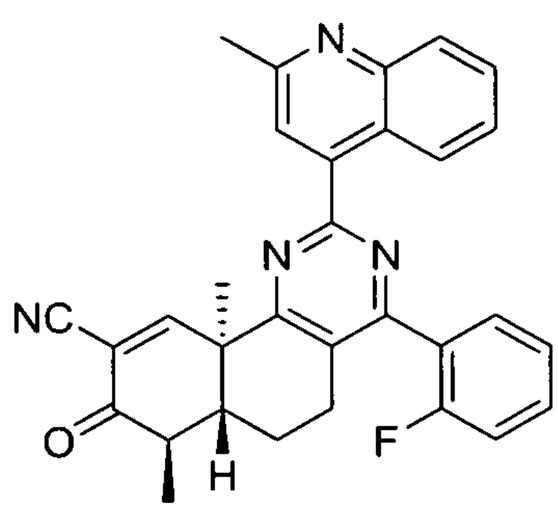
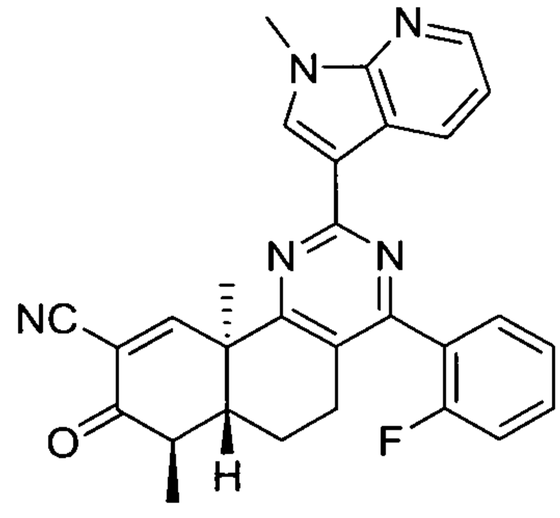
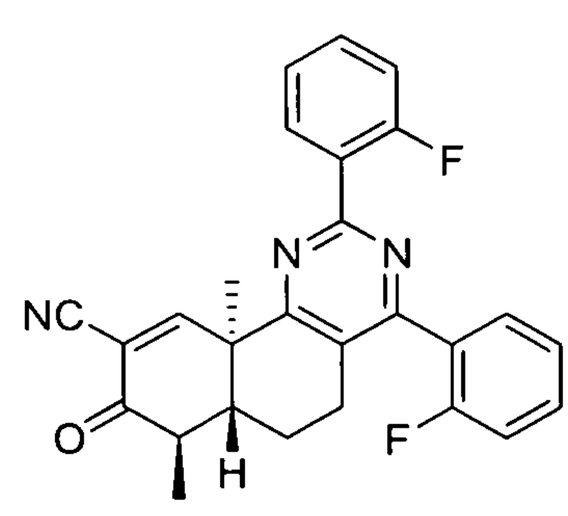
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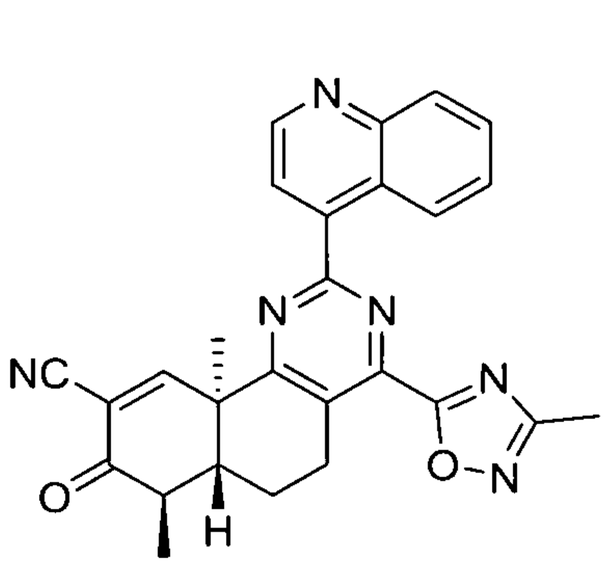
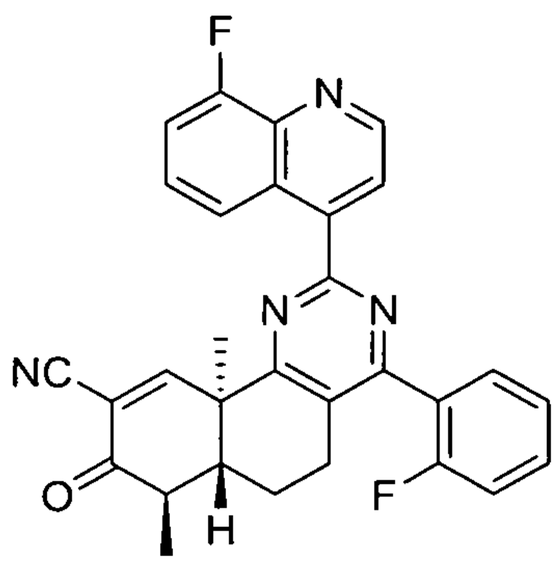
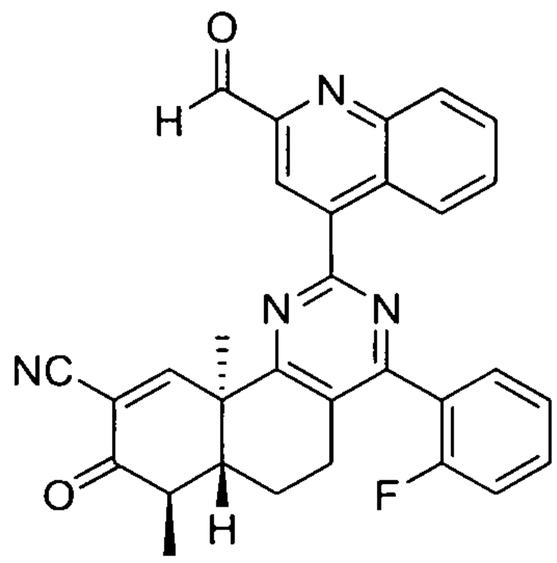
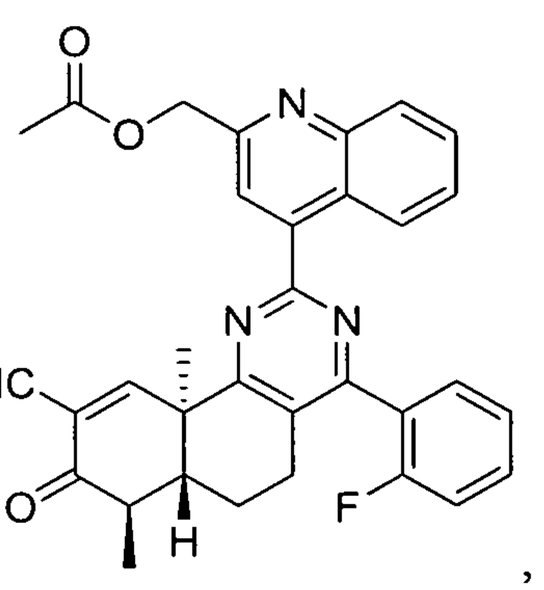
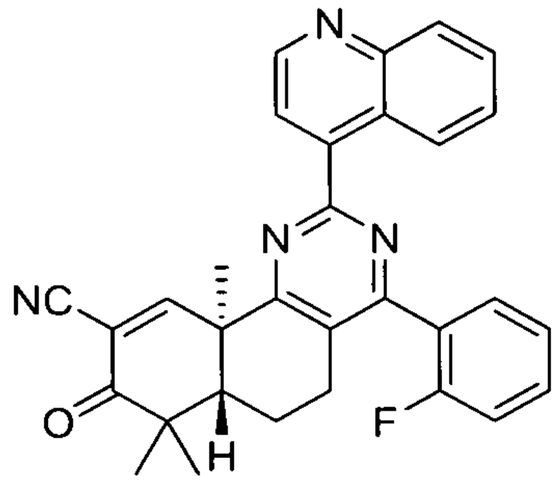
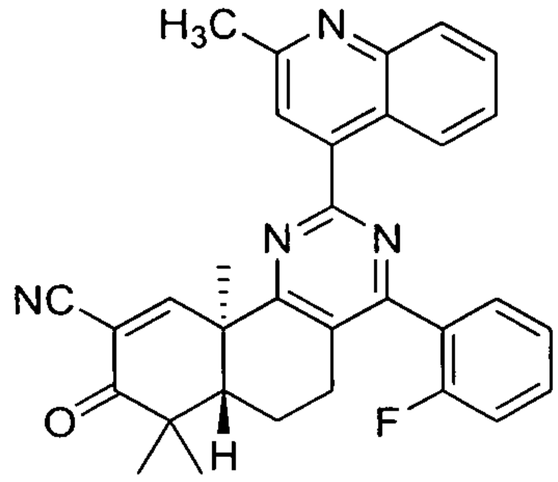
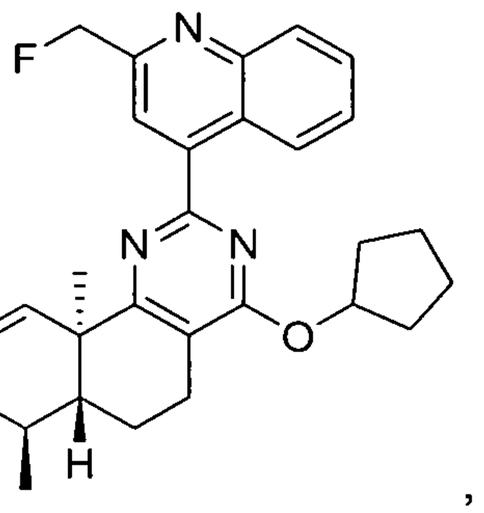
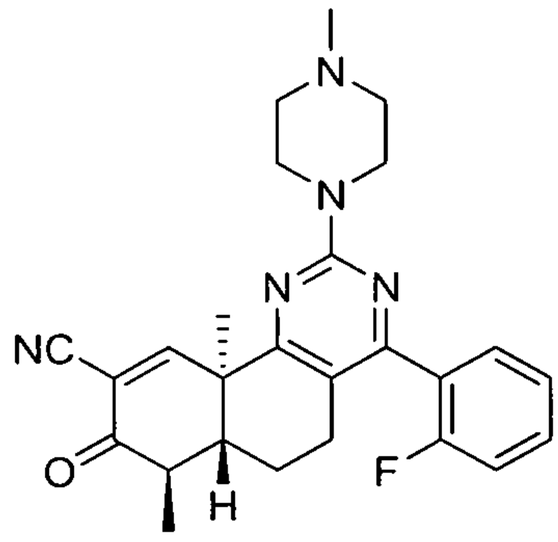
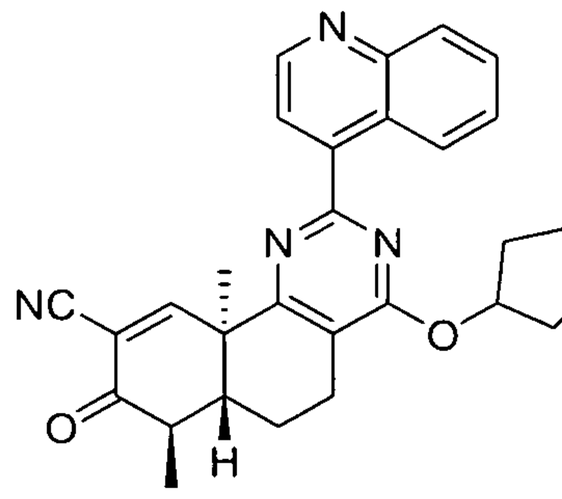
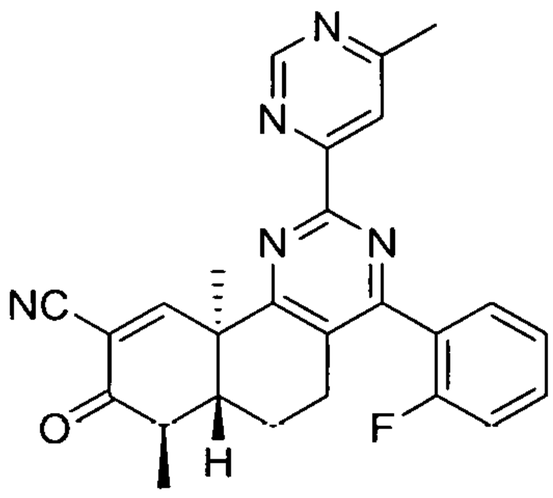
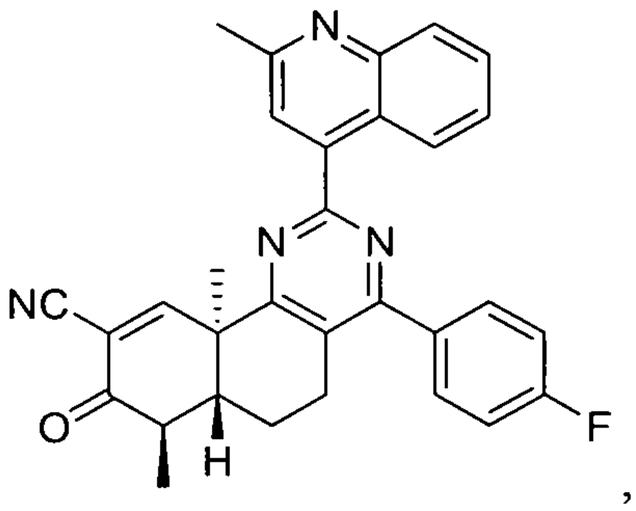
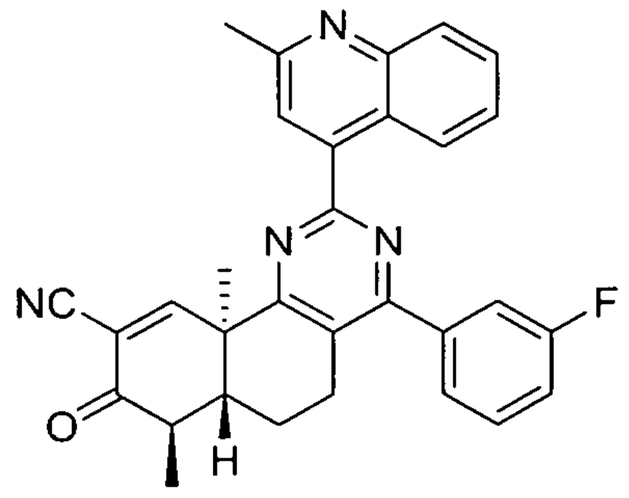
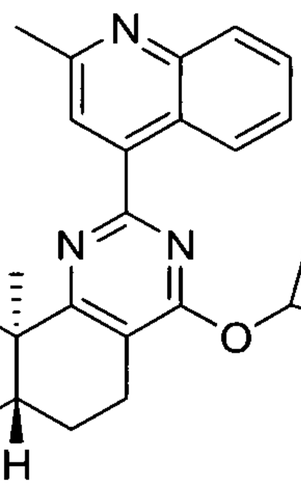
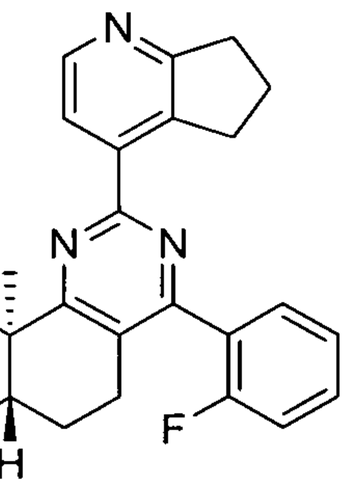
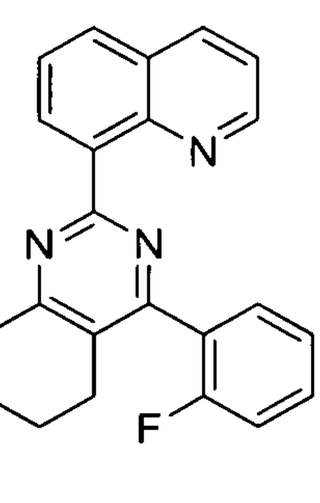
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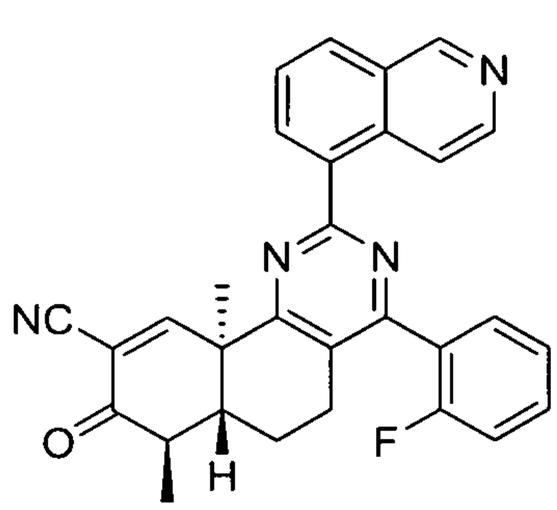
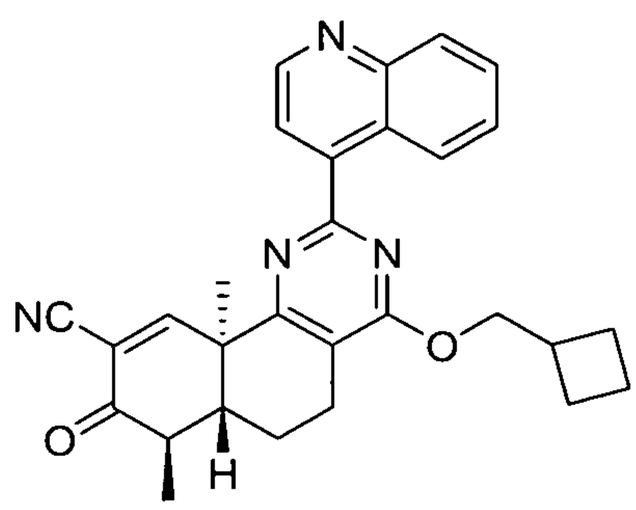
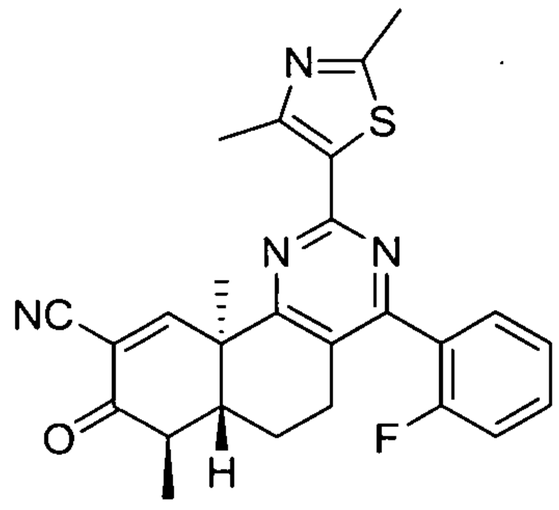
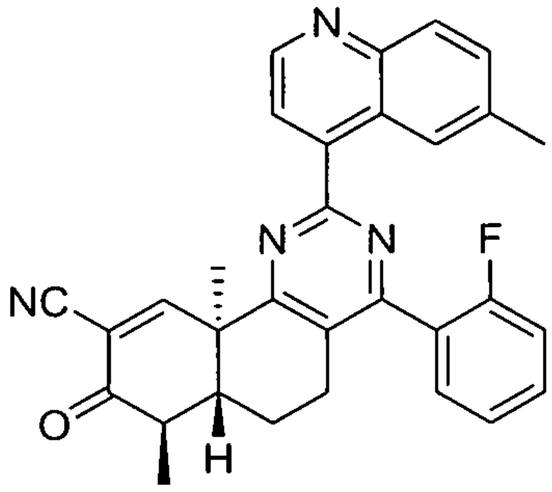
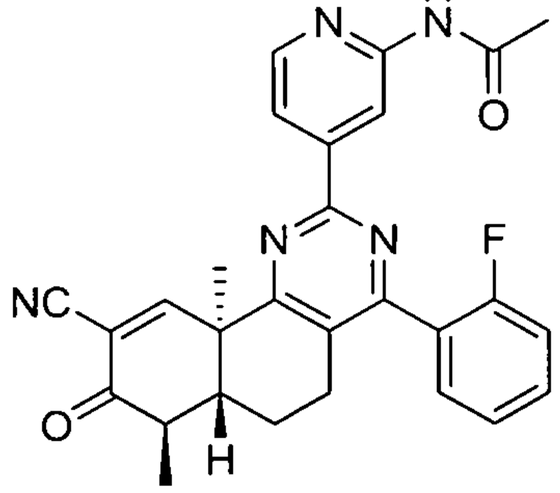
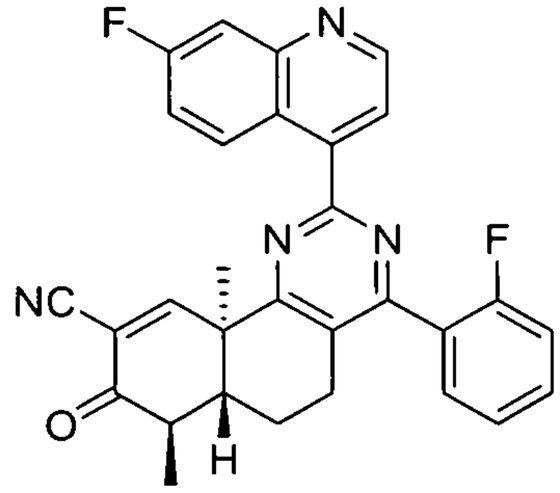
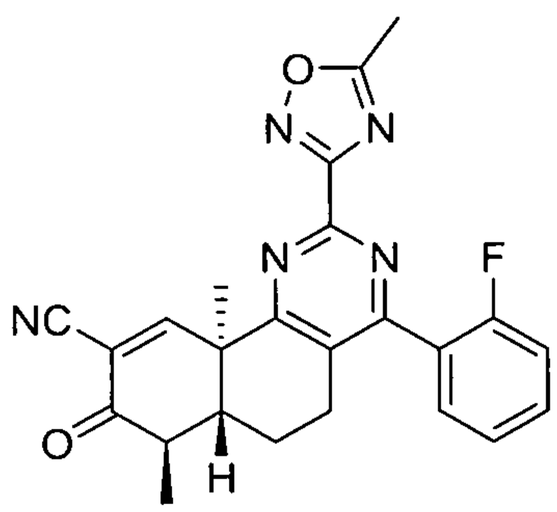
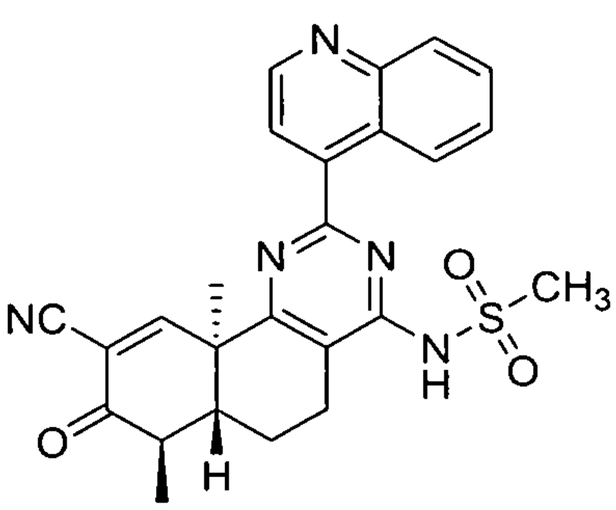
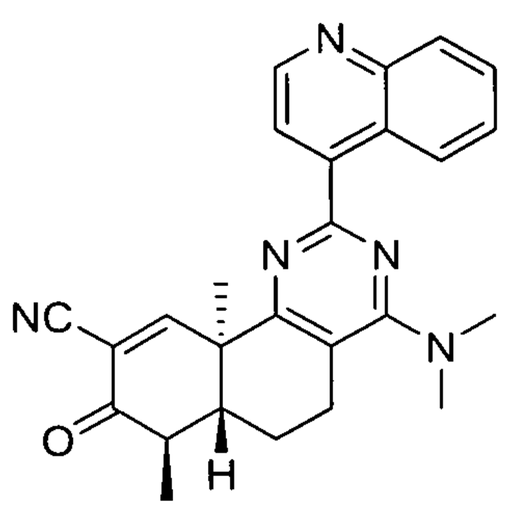
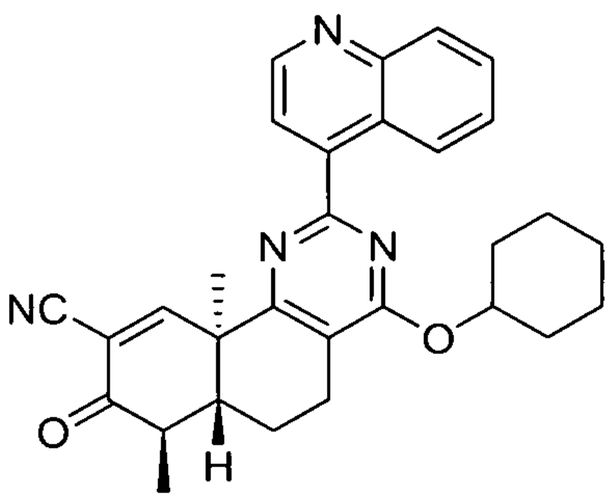
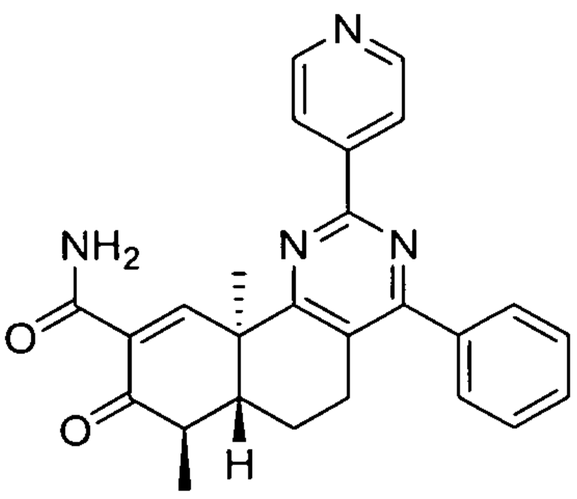
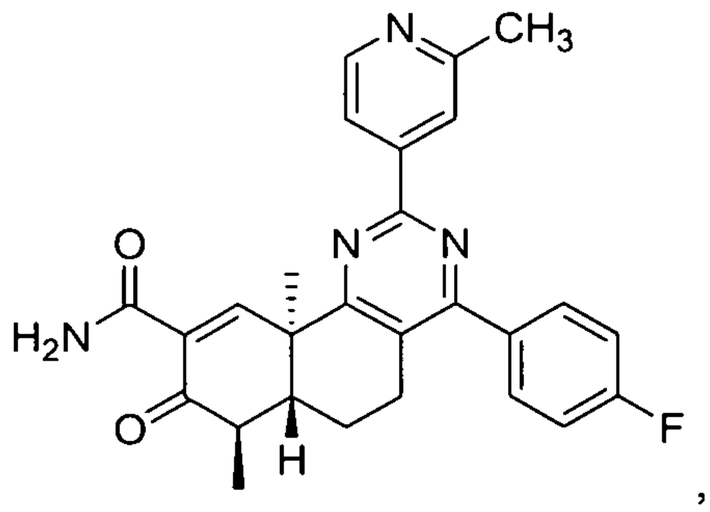
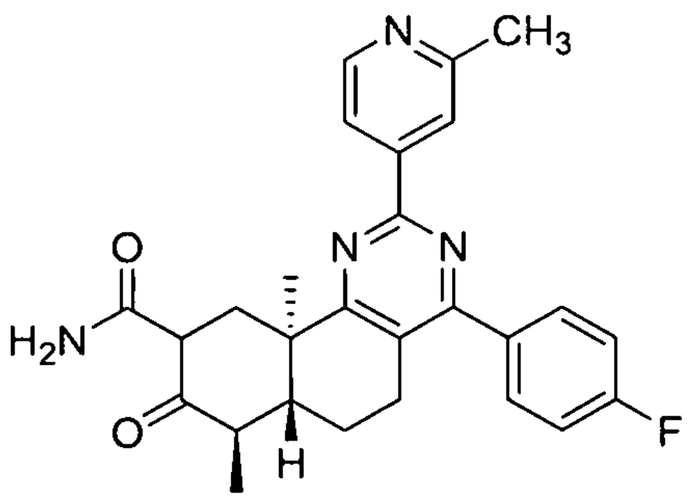
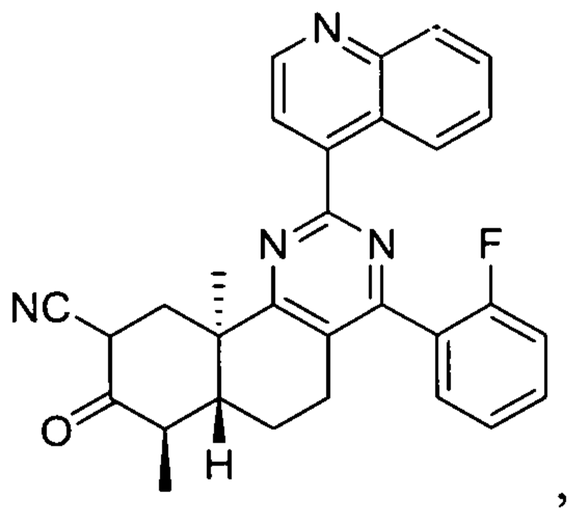
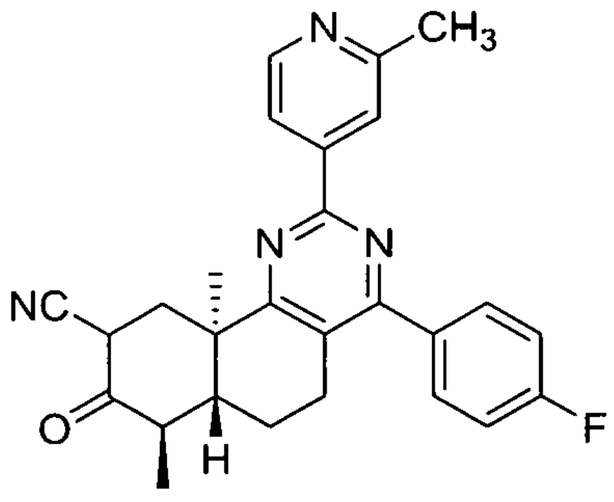

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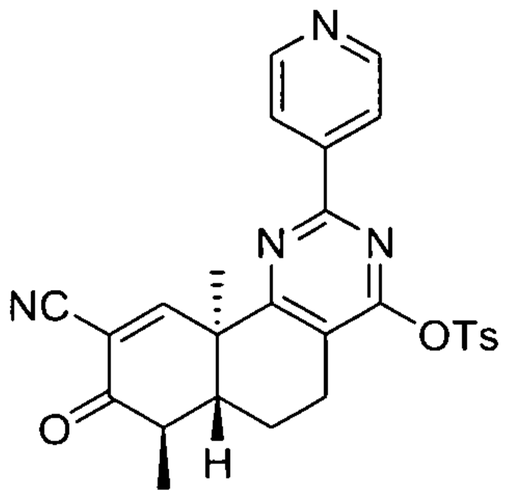
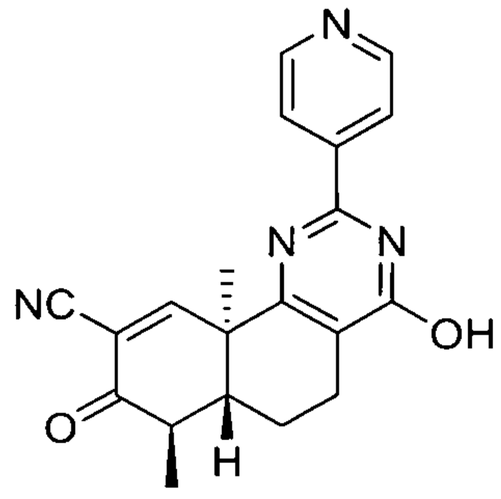
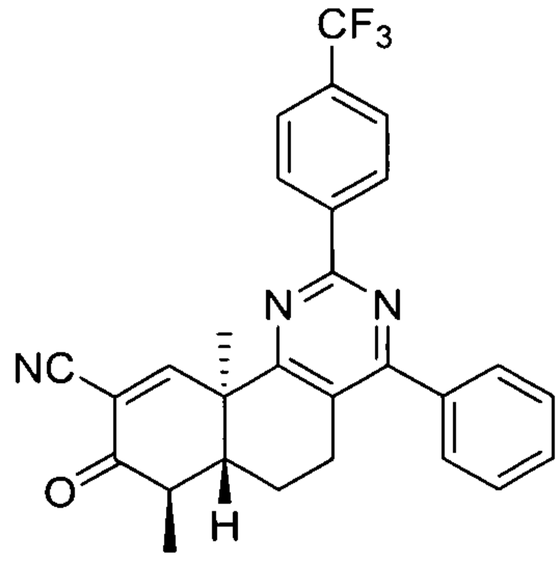
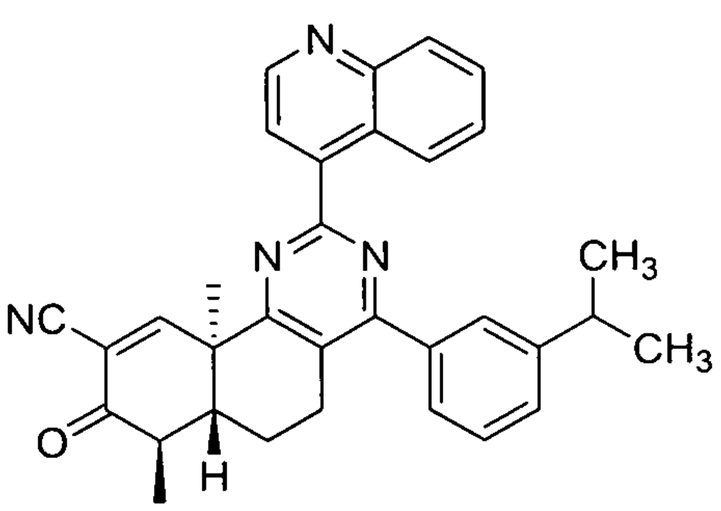
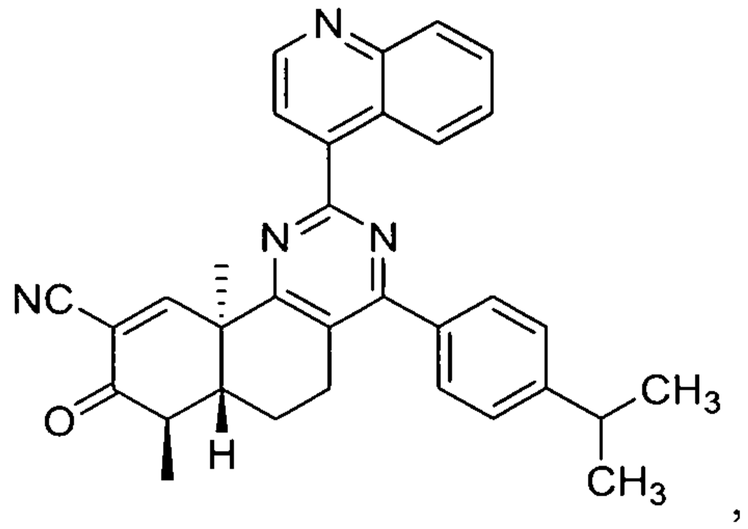
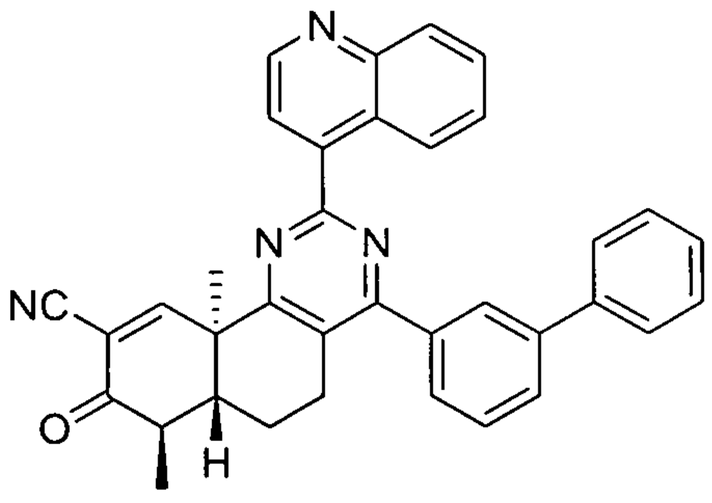
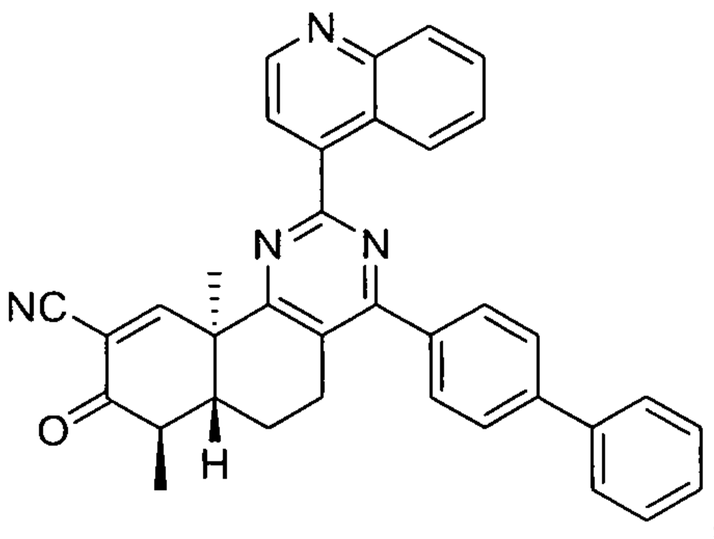
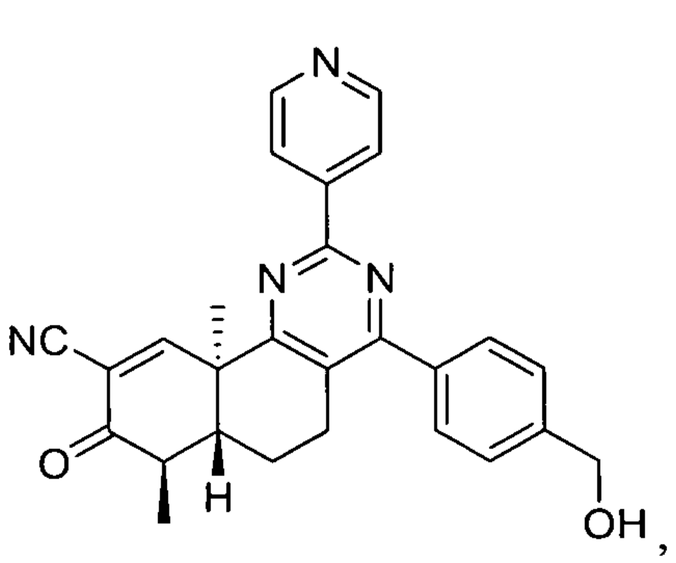
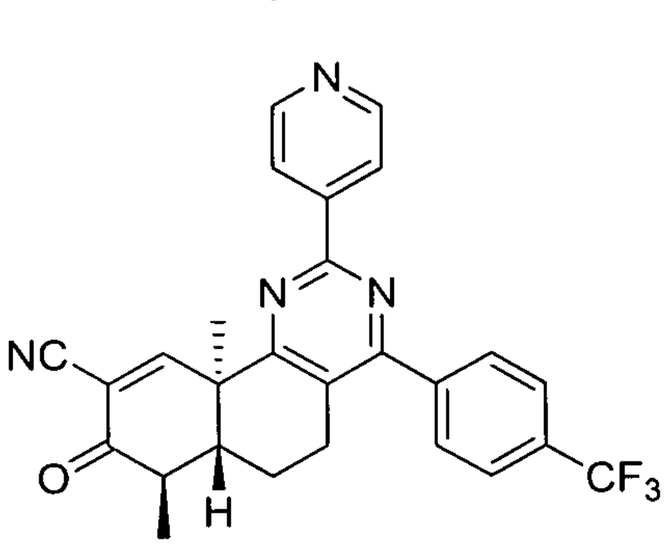
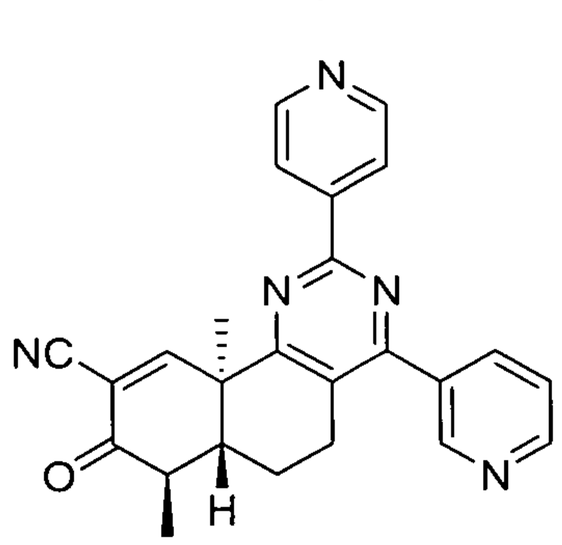
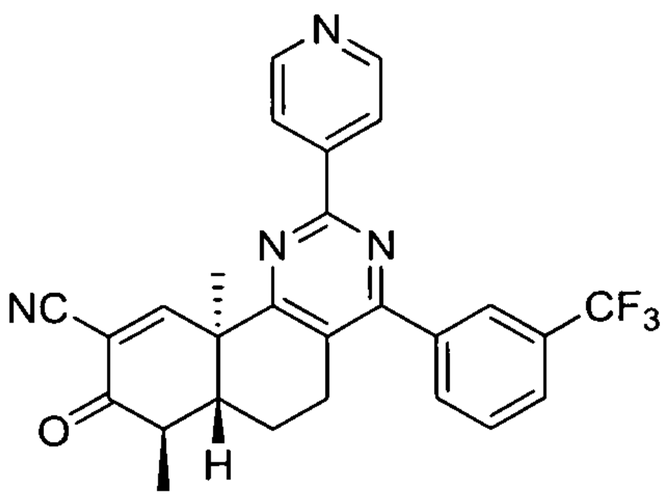
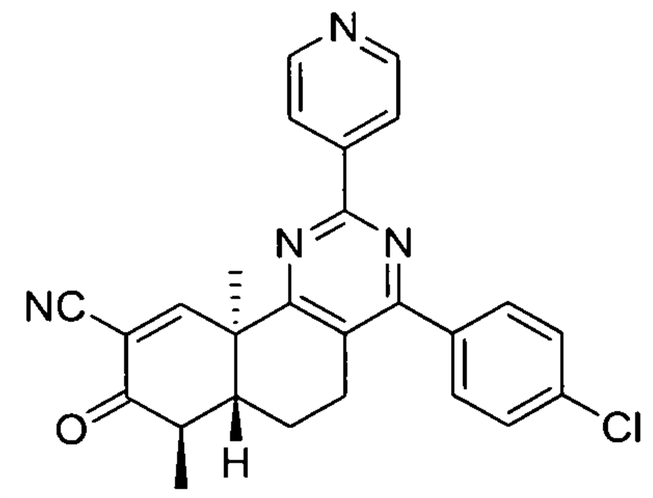
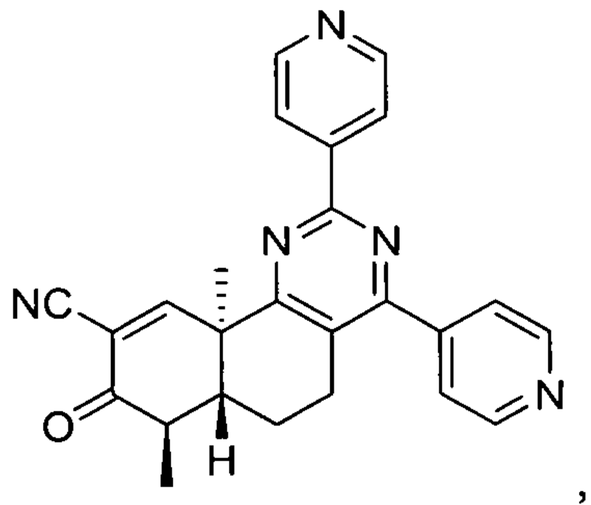

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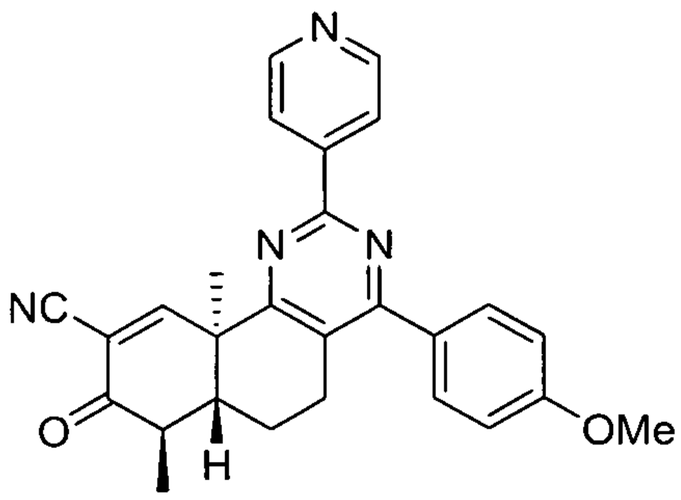
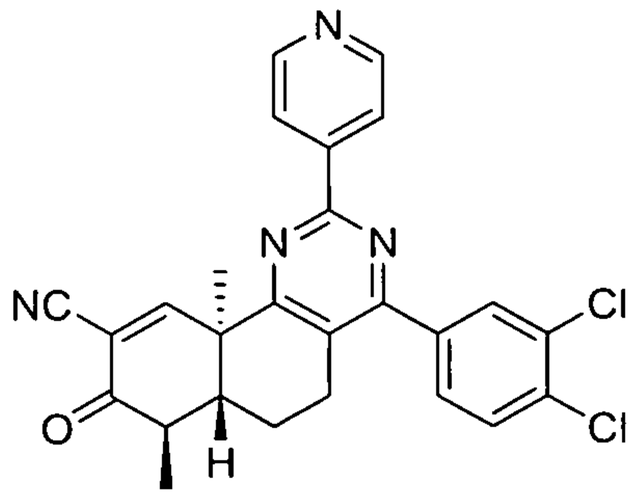
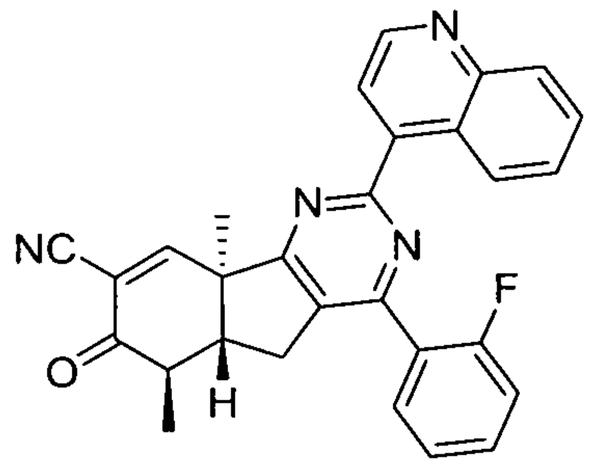
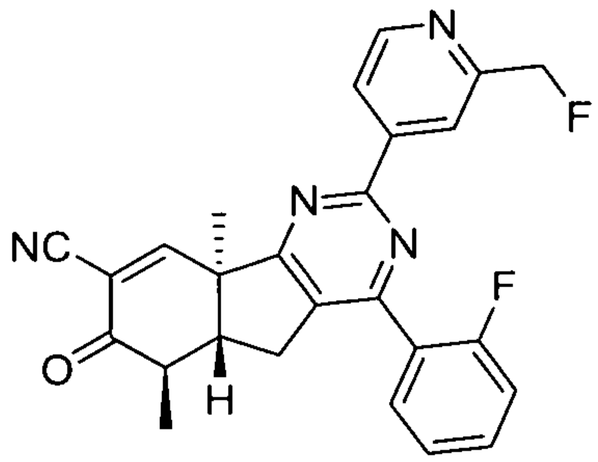
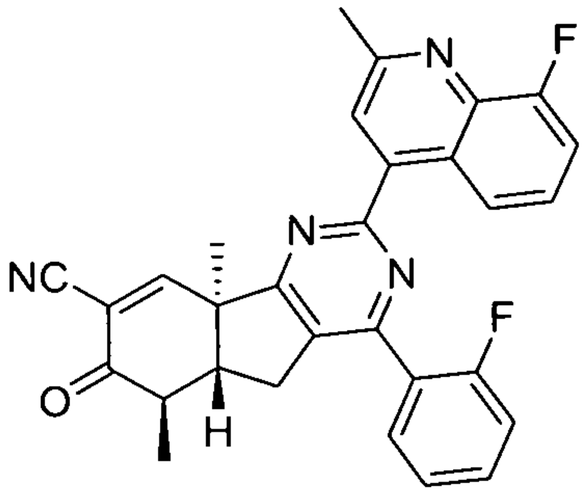
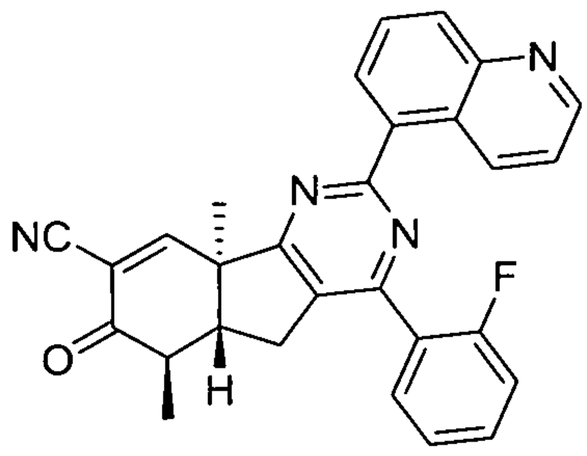
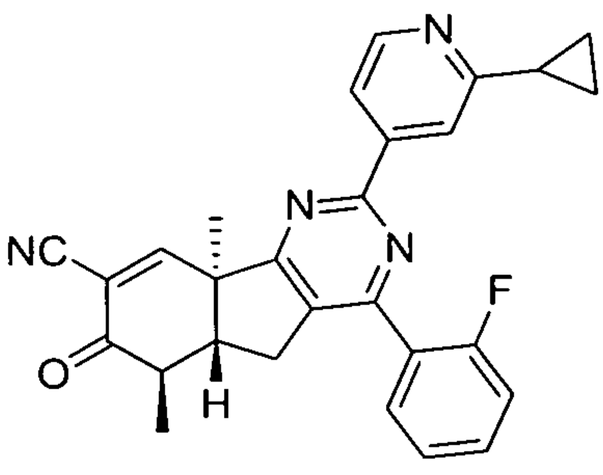
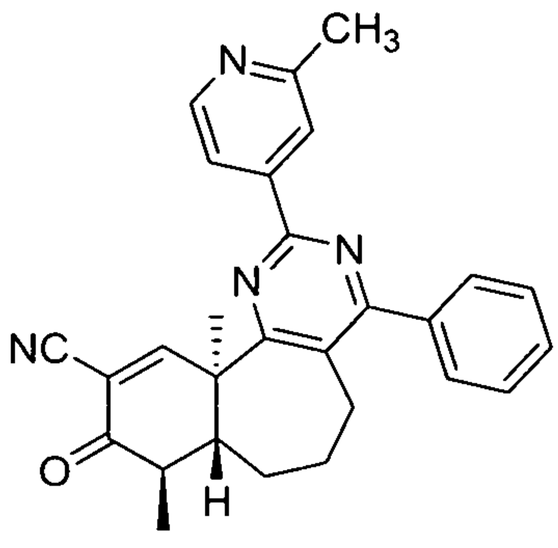
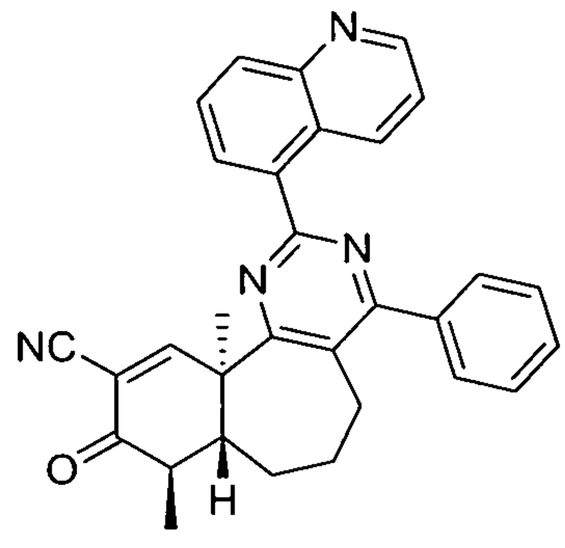
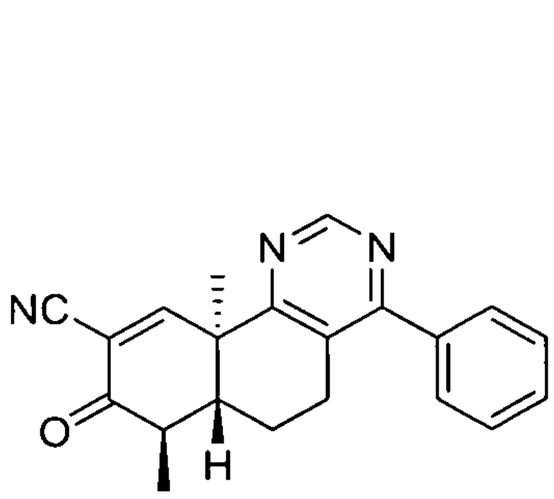
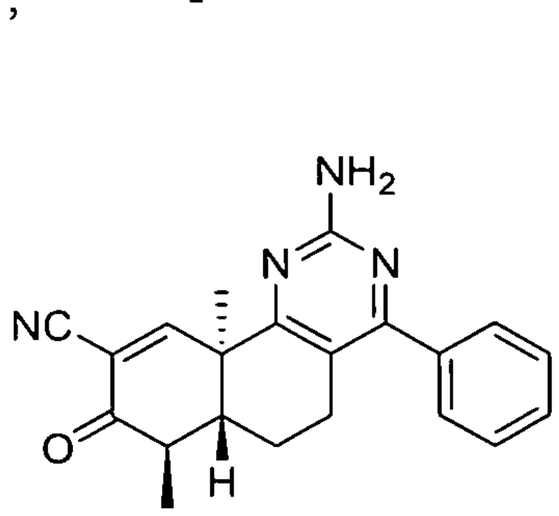
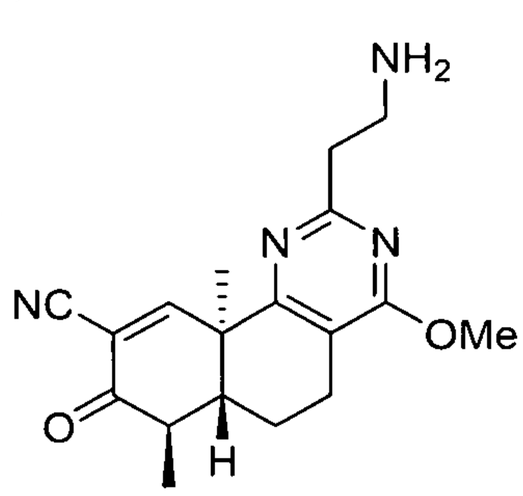
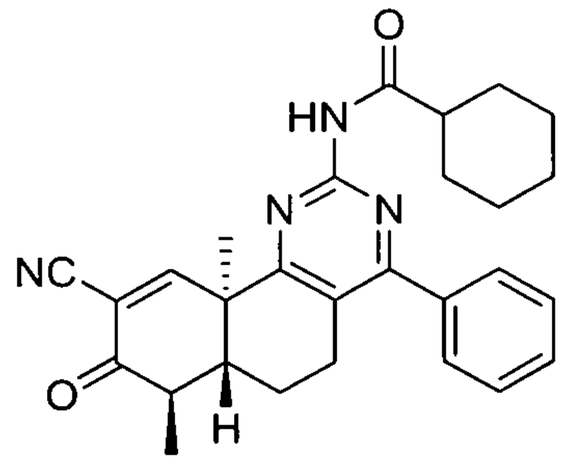

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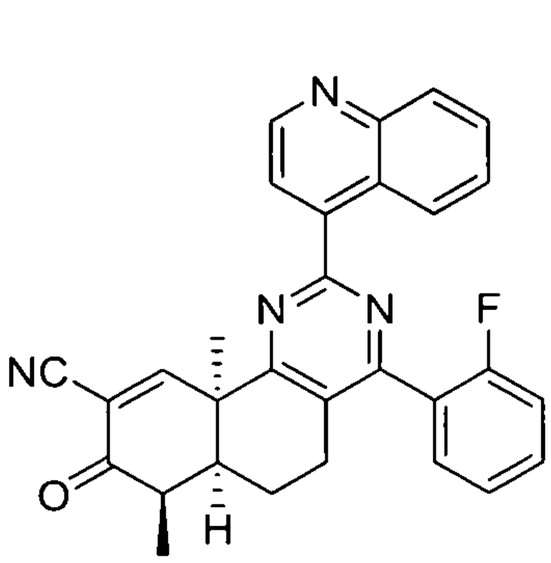
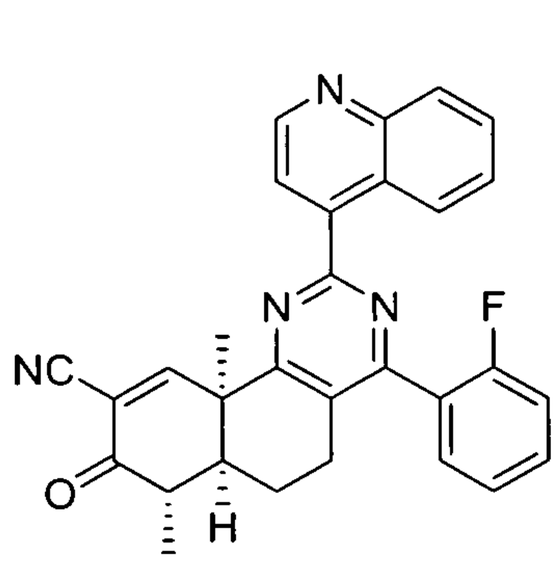
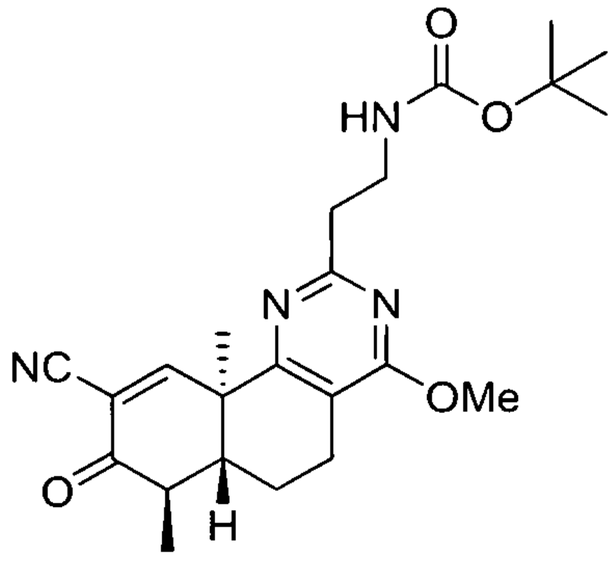
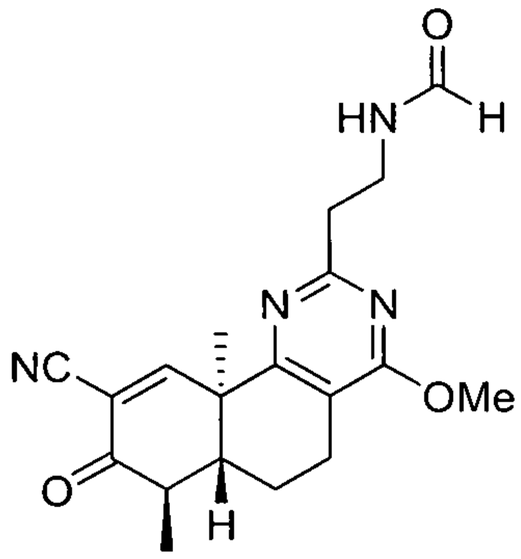
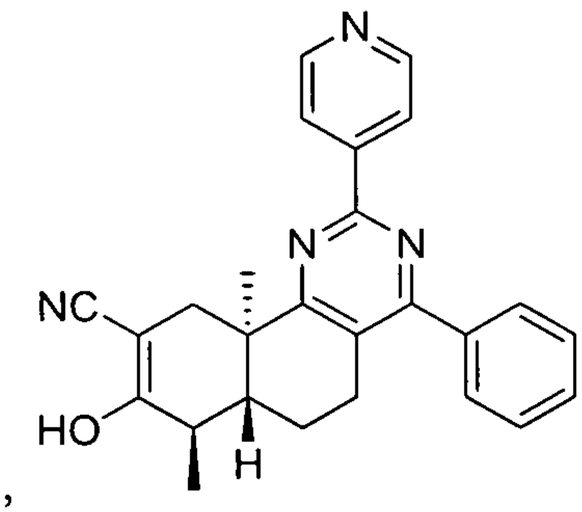
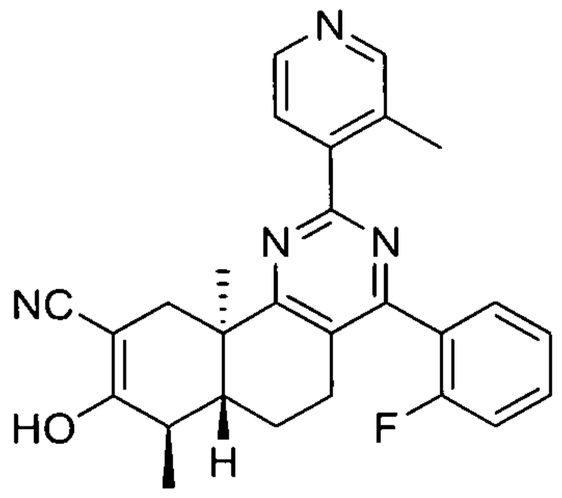
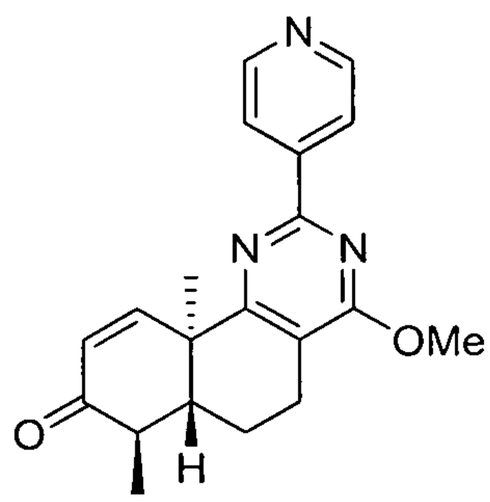
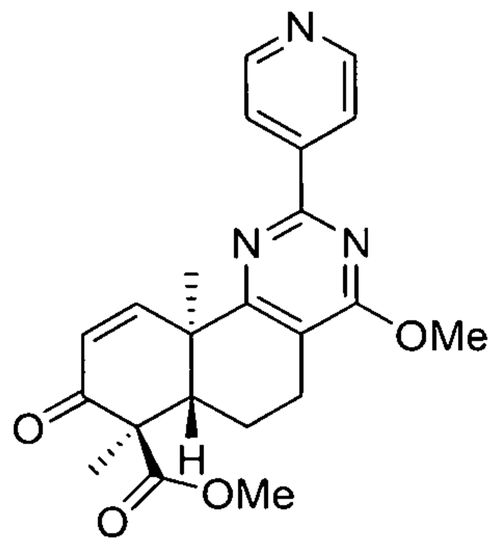

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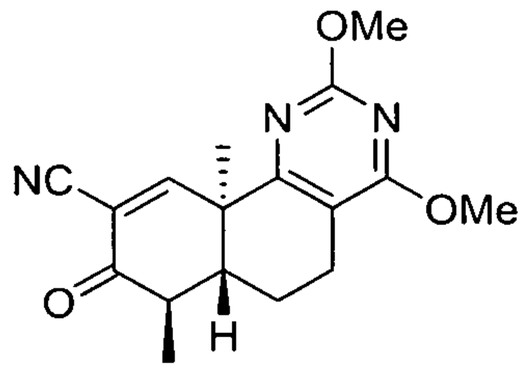
or a pharmaceutically acceptable salt thereof.

In still another aspect, the present disclosure provides compounds of the formula:


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or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure provides compounds of the formula:



or a pharmaceutically acceptable salt thereof.

In still yet another aspect, the present disclosure provides compounds further defined as:

(6a*R*,7*R*,10a*S*)-9-cyano-2,4-dimethoxy-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-2-(2-methoxypyridin-4-yl)-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(3-methylpyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(pyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-2-(2-fluoropyridin-4-yl)-9-cyano-4-methoxy-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(pyridin-3-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(pyridin-4-ylamino)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(6H)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(quinolin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

tert-butyl (2-((6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)ethyl)carbamate;

N-(2-((6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)ethyl)formamide;

(6a*R*,7*R*,10a*S*)-2-(2-aminoethyl)-9-cyano-4-methoxy-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(6H)-one;

(6a*R*,7*R*,10a*R*)-8-hydroxy-7,10a-dimethyl-4-phenyl-2-(pyridin-4-yl)-5,6,6a,7,10,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-7,9b-dimethyl-8-oxo-4-phenyl-2-(pyridin-4-yl)-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carboxamide;

(6a*R*,7*R*,10a*S*)-4-hydroxy-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-4-yl 4-methylbenzenesulfonate;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2,4-diphenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-(hydroxymethyl)phenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-cyclohexyl-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-4-(4-(trifluoromethyl)phenyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-(pyridin-3-yl)-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-4-(3-(trifluoromethyl)phenyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-4-(p-tolyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-chlorophenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*))-7,10a-dimethyl-8-oxo-2,4-di(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-methoxyphenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3,4-dichlorophenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-methoxypyridin-4-yl)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-amino-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)cyclohexanecarboxamide;

(6a*R*,7*R*,10a*S*)-4-benzyl-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(*R*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,8,10a-tetrahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-9-cyano-4-isopropoxy-7,10a-dimethyl-2-(quinolin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-isopropyl-7,10a-dimethyl-2-(quinolin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

tert-butyl 4-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)piperidine-1-carboxylate;

4-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)piperidin-1-ium chloride;

(6a*R*,7*R*,10a*S*)-2-(1-acetylpiperidin-4-yl)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

tert-butyl 5-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)-3,6-dihydropyridine-1(*2H*)-carboxylate;

5-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)-1,2,3,6-tetrahydropyridin-1-ium chloride;

(6a*R*,7*R*,10a*S*)-2-(1-acetyl-1,2,5,6-tetrahydropyridin-3-yl)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2,4-difluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(2-(trifluoromethyl)pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*R*)-4-(2-fluorophenyl)-8-hydroxy-7,10a-dimethyl-2-(3-methylpyridin-4-yl)-5,6,6a,7,10,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(3-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(3-fluoropyridin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(5-methylpyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-3-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-6-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)acetamide;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-8-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(8-fluoro-2-methylquinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-morpholinopyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(2-phenylpyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(isoquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(8-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2,4-dimethylthiazol-5-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(1-methyl-*1H*-pyrrolo[2,3-b]pyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(isoquinolin-1-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(7-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(8-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-methylpyrimidin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(pyridazin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6,7-dihydro-*5H*-cyclopenta[*b*]pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2,4-bis(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(2-(hydroxymethyl)pyridin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-5-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6-fluoro-2-methylquinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(isoquinolin-5-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(3,5-dimethylisoxazol-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-methylpyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(6-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6,8-difluoroquinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(4-methylpiperazin-1-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-morpholino-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclopropyl-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclobutoxy-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclobutylmethoxy)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclohexyloxy)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-4-yl)methanesulfonamide;

(6a*R*,7*R*,10a*S*)-4-(dimethylamino)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3,5-dimethylisoxazol-4-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-benzyl-4-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-4-yl)-*N*-methylbenzamide;

(6a*R*,7*R*,10a*S*)-4-(furan-2-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(benzofuran-2-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-4-(5-methylfuran-2-yl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-4-(3-methyl-1,2,4-oxadiazol-5-yl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-4-(thiazol-2-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-fluorophenyl)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclobutoxy-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclobutoxy-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-(fluoromethyl)quinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(2-formylquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)quinolin-2-yl)methyl acetate;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-7,7,10a-trimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-2-(2-(fluoromethyl)quinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-2-(8-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-2-(2-(fluoromethyl)quinolin-4-yl)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(2-isopropylquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-7-propyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-7-ethyl-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-2-(8-fluoroquinolin-4-yl)-7,7,10a-trimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(*R*)-4-(2-fluorophenyl)-2-(8-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,8,10a-tetrahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-2-(7-fluoroquinolin-4-yl)-7,9b-dimethyl-8-oxo-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,9b-dimethyl-8-oxo-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-2-(isoquinolin-4-yl)-7,9b-dimethyl-8-oxo-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-7,9b-dimethyl-8-oxo-2-(quinolin-4-yl)-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*S*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-7,7,9b-trimethyl-8-oxo-2-(quinolin-4-yl)-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,10a*R*)-4-methoxy-7,10a-dimethyl-2-(pyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

methyl (6aS,7R,10aR)-4-methoxy-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-7-carboxylate;

(6a*S*,7*R*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7-(3-hydroxypropyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-7-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-(pyrrolidin-1-yl)-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(4-acetylpiperazin-1-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6-cyclopropylpyridin-3-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(6-phenylpyridin-3-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-(2-(methylsulfonyl)ethyl)pyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-((methylsulfonyl)methyl)pyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-(2-(methylsulfonyl)ethyl)pyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7-allyl-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-10a-methyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-10a-methyl-8-oxo-7-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7-methyl-8-oxo-10a-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7-methyl-8-oxo-10a-phenyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-2-(quinolin-5-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)propanoic acid;

ethyl 3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)propanoate;

3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)-*N*,*N*-dimethylpropanamide;

(6a*R*,7*R*,10a*S*)-2-(2-(2-(ethylsulfonyl)ethyl)pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-((ethylsulfonyl)methyl)pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-8-oxo-10a-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-4-(2-fluorophenyl)-8-oxo-10a-propyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-7-(cyclopropylmethyl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-10a-methyl-8-oxo-7-propyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-10a-methyl-8-oxo-7-propyl-2-(quinolin-5-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-isopropylphenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-isopropylphenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-([1,1'-biphenyl]-3-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-([1,1'-biphenyl]-4-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-4-(2-fluorophenyl)-10a-isopentyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-10a-isopentyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-4-(2-fluorophenyl)-7,10a-dimethyl-7-(2-methylallyl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-8-oxo-10a-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-8-oxo-7,10a-dipropyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7-methyl-8-oxo-10a-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(5a*R*,6*R*,9a*S*)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-2-(quinolin-4-yl)-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-2-(8-fluoro-2-methylquinolin-4-yl)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-2-(quinolin-5-yl)-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(6a*S*,7*S*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)propanamide;

N-(2-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)ethyl)acetamide;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(3-phenylpyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(3-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-7-ethyl-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(7a*R*,8*R*,11a*S*)-8,11a-dimethyl-2-(2-methylpyridin-4-yl)-9-oxo-4-phenyl-6,7,7a,8,9,11a-hexahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-10-carbonitrile;

(7a*R*,8*R*,11a*S*)-8,11a-dimethyl-9-oxo-4-phenyl-2-(quinolin-5-yl)-6,7,7a,8,9,11a-hexahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-10-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carboxamide;

(6a*R*,7*R*,10a*R*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline-9-carboxamide; and

(6a*R*,7*R*,10a*R*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline-9-carbonitrile;

or a pharmaceutically acceptable salt thereof.

In still another aspect, the present disclosure provides pharmaceutical compositions comprising:

(A) a compound described herein; and

(B) an excipient.

In some embodiments, the pharmaceutical compositions are formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous

infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion. In some embodiments, the pharmaceutical compositions are formulated for oral administration. In other embodiments, the pharmaceutical compositions are formulated for administration via injection. In other embodiments, the pharmaceutical compositions are formulated for intraarterial administration, intramuscular administration, intraperitoneal administration, or intravenous administration. In other embodiments, the pharmaceutical compositions are formulated for administration topically such as for topical administration to the skin or to the eye. In other embodiments, the pharmaceutical compositions are formulated as a unit dose.

In yet another aspect, the present disclosure provides methods of treating or preventing a disease or disorder in a patient in need thereof comprising administering to the patient a pharmaceutically effective amount of a compound or composition described herein. In some embodiments, the patient is a mammal such as a human. In some embodiments, the disease or disorder is associated with increased production of cytokine IL-17. In some embodiments, the disease or disorder is associated with dysregulated angiogenesis.

In some embodiments, the disease or disorder is an autoimmune disease, organ rejection, asthma, cancer, a neurological disorder, a psychiatric disorder, a neuropsychiatric disorder, chronic pain syndrome, an inflammatory condition, a retinal disorder, or a cardiovascular disease. In some embodiments, the disease or disorder is cancer In some embodiments, the disease or disorder is an autoimmune disease such as psoriasis, multiple sclerosis, scleroderma, rheumatoid arthritis, lupus, psoriatic arthritis, ankylosing spondylitis, Sjögren syndrome, vitiligo, uveitis, dry eye syndrome, systemic sclerosis, type 1 diabetes, myasthenia gravis, and inflammatory bowel disease. In other embodiments, the disease or disorder is a cardiovascular disease such as vasculitis, atherosclerosis, myocardial infarction, myocarditis, heart failure, pulmonary hypertension, or stroke. In other embodiments, the disease or disorder is a neurological disorder such as epilepsy, multiple sclerosis, spinal cord injury, Guillain-Barre syndrome, or another neurological disorder involving dysregulated inflammatory signaling. In other embodiments, the disease or disorder is a neurodegenerative disorder such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease. In other embodiments, the disease or disorder is an inflammatory condition such as pancreatitis, hepatitis, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, dermatitis, gastritis, esophagitis, irritable bowel syndrome, inflammatory bowel disease, nephritis, muscle wasting, or osteoarthritis. In other embodiments, the disease or disorder is a chronic pain syndrome such as fibromyalgia or neuropathic pain. In other embodiments, the disease or disorder is a severe inflammatory response to a pathogen such as from encephalitis, meningitis, *H. pylori*, *Toxoplasma gondii*, or *Leishmania spp.* In other embodiments, the disease or disorder is obesity or a condition associated with obesity. In some embodiments, the condition associated with obesity is insulin resistance or fatty liver disease. In some embodiments, the retinal disorder is macular degeneration or another disorder of the retina.

In some embodiments, the disease or disorder is associated with inflammation. In some embodiments, the disease or disorder associated with inflammation is obesity, Type 2 diabetes, or a

complication of Type 1 or Type 2 diabetes. In some embodiments, the complication of Type 1 or Type 2 diabetes is neuropathy, reduced kidney function or chronic kidney disease, retinopathy, diabetic ulcers, or cardiovascular disease. In other embodiments, the disease or disorder associated with inflammation is chronic kidney disease. In some embodiments, the chronic kidney disease is hereditary. In other embodiments, the chronic kidney disease is due to a non-hereditary cause.

In some embodiments, the methods comprise administering the compound once. In other embodiments, the methods comprise administering the compound two or more times.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula doesn't mean that it cannot also belong to another generic formula.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Disclosed herein are new compounds and compositions that may be used to inhibit the activity of the RORγ nuclear receptor and/or IL-17 and are thus useful in the treatment of a wide variety of different indications such as autoimmune disease, metabolic diseases, cancer, and infections. In some embodiments, these compounds may be used to modulate the expression of one or more downstream compound such as interleukin-17 (IL-17), prevent or inhibit excessive production of IL-17, reduce circulating levels of IL-17, and/or prevent or treat wide range of diseases or disorders, including those with inflammatory and autoimmune-related components.

I. Compounds and Synthetic Methods

The compounds of the present invention (also referred to as "compounds of the present disclosure") are shown, for example, above, in the summary of the invention section, and in the claims below. They may be made using the synthetic methods outlined in the Examples section. These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in Smith, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* (2013), which is incorporated by reference herein. In addition, the synthetic methods may be further modified and optimized for preparative, pilot- or large-scale production, either batch or continuous, using the principles and techniques of process chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in Anderson, *Practical Process Research & Development – A Guide for Organic Chemists* (2012), which is incorporated by reference herein.

All of the compounds of the present invention may be useful for the prevention and treatment of one or more diseases or disorders discussed herein or otherwise. In some embodiments, one or more of the compounds characterized or exemplified herein as an intermediate, a metabolite, and/or prodrug, may nevertheless also be useful for the prevention and treatment of one or more diseases or disorders. As such unless explicitly stated to the contrary, all of the compounds of the present invention are deemed "active compounds" and "therapeutic compounds" that are contemplated for use as active pharmaceutical ingredients (APIs). Actual suitability for human or veterinary use is typically determined using a combination of clinical trial protocols and regulatory procedures, such as those administered by the Food and Drug Administration (FDA). In the United States, the FDA is responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices.

In some embodiments, the compounds of the present invention have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (*e.g.*, higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the indications stated herein or otherwise.

Compounds of the present invention may contain one or more asymmetrically-substituted carbon or nitrogen atoms, and may be isolated in optically active or racemic form. Thus, all chiral, diastereomeric, racemic form, epimeric form, and all geometric isomeric forms of a chemical formula are intended, unless the specific stereochemistry or isomeric form is specifically indicated. Compounds may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. In some embodiments, a single diastereomer is obtained. The chiral centers of the compounds of the present invention can have the *S* or the *R* configuration. In some embodiments, the present compounds may contain two or more atoms which have a defined stereochemical orientation.

In one aspect, the compounds of the present invention contain at least one stereogenic centers at carbon atoms 4, 5, and 10. In some embodiments, carbon atom 10 is in the *S* configuration. In some embodiments, the compounds of the present invention contain a stereogenic center at carbon atom 5, provided that carbon atom 5 is not part of a double bond. In some of these embodiments carbon atom 5 is in the *R* configuration. In some embodiments, the compounds of the present invention contain a stereogenic center at carbon atom 4, provided that carbon atom 4 is not a part of a double bond. In some of these embodiments, carbon atom 4 is in the *R* configuration.

Without being bound by theory, in some embodiments, the compounds provided herein which exhibit a specific stereocheical orientation at carbon atoms 4, 5, and/or 10 exhibit retained inhibition of hIL17 while exhibiting reduced NRF2 activation relative to compound with a different stereocheical orientation at carbon atoms 4, 5, and/or 10. In some embodiments, the present disclosure provides compounds exhibiting a lower IC_{50} for inhibition of hIL17 as measure by determining the concentration required to inhibit using fluorescently tagged anti-IL17 antibodies, for example, as described in Example 2 when compared to the two fold activation of NRF2. In some embodiments, the present disclosure provides compounds exhibiting an increase in hIL17 inhibition when compared to the two fold NRF2 activation value when the 2-fold NRF2 activation is measured by determining the concentration requirement to increase GST ARE Luciferase reporter activity by 2-fold in AREc32 cells relative to DMSO treated cells, for example, as described in Example 2.

Chemical formulas used to represent compounds of the present invention will typically only show one of possibly several different tautomers. For example, many types of ketone groups are known to exist in equilibrium with corresponding enol groups. Similarly, many types of imine groups exist in equilibrium with enamine groups. Regardless of which tautomer is depicted for a given compound, and regardless of which one is most prevalent, all tautomers of a given chemical formula are intended.

In addition, atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

Compounds of the present invention may also exist in prodrug form. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, *etc.*), the compounds employed in some methods of the invention may, if desired, be

delivered in prodrug form. Thus, the invention contemplates prodrugs of compounds of the present invention as well as methods of delivering prodrugs. Prodrugs of the compounds employed in the invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a hydroxy, amino, or carboxylic acid, respectively.

It should be recognized that the particular anion or cation forming a part of any salt form of a compound provided herein is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002), which is incorporated herein by reference.

It will appreciated that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates." Where the solvent is water, the complex is known as a "hydrate." It will also be appreciated that many organic compounds can exist in more than one solid form, including crystalline and amorphous forms. All solid forms of the compounds provided herein, including any solvates thereof are within the scope of the present invention.

II. Diseases Associated with Inflammatory Cytokine IL-17

Various reports have implicated the inflammatory cytokine IL-17 in the pathogenesis of many autoimmune diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis, inflammatory bowel diseases (including but not limited to Crohn's disease), multiple sclerosis, autoimmune nephritis, autoimmune uveitis, Type 1 diabetes, and ankylosing spondylitis. In some embodiments, the compounds provided herein may be administered to a patient in order to treat or prevent one or more of these diseses or disorders. A type of T lymphocyte known as a Th17 cell is a primary source of IL-17. There are multiple members of the IL-17 family. The first identified member, IL-17A, is commonly referred to as IL-17. IL-17 is composed of two monomers linked by disulfide bonds to form a homodimer (Miossec and Kolls, 2012). Aside from IL-17A, the other principal family member is IL-17F. Some evidence suggests that IL-17F and IL-17A, though they have many effects in common, may have different effects in certain settings such as lung inflammation. The IL-17 cytokines bind to IL-17 receptors (IL-17R) located in the membrane of select cell types. Although there are multiple subtypes of the IL-17 receptor, the IL-17RA/IL-17RC complex is required for the activity of IL-17A and IL-17F. IL-17RA has the unusual property of signaling through a pathway that involves an adaptor protein (ACT1) rather than the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway employed by most interleukin receptors. Binding of IL-17A to IL-17RA activates the pro-inflammatory nuclear factor-kappa B (NF-κB) pathway and pro-inflammatory elements of the mitogen-activated protein kinase (MAPK) pathway such as JUN N-terminal kinase (JNK), p38 and extracellular signal-related kinase

(ERK). IL-17 activity stimulates secretion of IL-6 and IL-8 from mesenchymal cells and leads to fever along with the accumulation of neutrophils in blood and tissue. In some embodiments, the compounds provided herein may be used to inhibit the secretion of IL-6 and IL-8 from mesenchymal cells. In some embodiments, the compounds provided herein may be administered to a patient in order to prevent or inhibit fever in a patient. In some embodiments, the compounds provided herein may be administered to a patient in order to prevent the accumulation of neutrophils in the blood or tissue of the patient.

Aside from its contribution to acute inflammation, IL-17 also contributes to chronic inflammation (Miossec and Kolls, 2012). In some embodiments, the compounds provided herein may be administered to a patient in order to prevent or treat chronic inflammation. IL-17 stimulates the production of matrix metalloproteinases (MMPs), which among other effects can degrade cartilage in joints. In some embodiments, the compounds provided herein may be administered to a patient in order to prevent or treat degradation of the patient's cartilage. IL-17 also increases the expression of receptor activator of NF-κB ligand (RANKL) in osteoblasts, leading to differentiation and activation of osteoclasts and bone degradation. In some embodiments, the compounds provided herein may be administered to a patient in order to prevent or treat degradation of the patient's bone. Depending on the target cell that is exposed to it, IL-17 may stimulate the production of IL-6, IL-8, IL-1, tumor necrosis factor (TNF), MMPs, nitric oxide, or several other proteins that are implicated in inflammatory conditions (*e.g.*, tissue factor, CCL20, G-CSF and GM-CSF). In some embodiments, the compounds provided herein may be administered to a patient in order to inhibit the production of IL-6, IL-8, IL-1, tumor necrosis factor (TNF), MMPs, nitric oxide, or several other proteins that are implicated in inflammatory conditions (*e.g.*, tissue factor, CCL20, G-CSF and GM-CSF).

Although IL-17 plays a role in the immune response to invading pathogens, excessive IL-17 activity has been implicated in pathologies associated with an excessive immune response to an infection. In some embodiments, the compounds provided herein may be administered to a patient in order to prevent or treat excessive immune response to an infection. For example, IL-17 has been implicated in the severe neuroinflammation associated with *Toxoplasma gondii* infection and increased severity of lesions associated with *Leishmania* infection. In some embodiments, the compounds provided herein may be administered to a patient in order to treat or prevent neuroinflammation, for example, neuroinflammation associated with *Toxoplasma gondii* infection. In some embodiments, the compounds provided herein may be administered to a patient in order to treat or prevent lesions associated with *Leishmania* infection. In these and other cases, IL-17 appears to play a role in perpetuating the infection, promoting an excessive inflammatory response, and inhibiting clearance of the infectious agent (Waite and Skokos, 2012). In some embodiments, the compounds provided herein may be administered to a patient in order to prevent an excessive inflammatory response and/or promote the clearance of an infectious agent.

Drugs targeting IL-17 have entered clinical trials for a wide variety of inflammatory conditions, including psoriasis, rheumatoid arthritis, ankylosing spondylitis, uveitis, Behcet's disease, psoriatic arthritis, Crohn's disease, polymyalgia rheumatica, dry eye syndrome, multiple sclerosis, graft-versus-

host disease, and asthma. In some embodiments, the compounds provided herein may be administered to a patient in order to treat or prevent one or more of these diseses or disorders. Preclinical evidence also implicates IL-17 in the pathology of type 1 diabetes, and Th17 cells are elevated in patients with adult onset Still's disorder, another autoimmune disease. In some embodiments, the compounds provided herein may be administered to a patient in order to treat type 1 diabetes. In some embodiments, the compounds provided herein may be administered to a patient in order to treat or prevent adult onset Still's disorder. Activity of Th17 cells has been implicated in the development of graft-versus-host disease following allogeneic stem cell (*e.g.*, bone marrow) transplantation (Fujiwara, *et al.*, 2014). In some embodiments, the compounds provided herein may be administered to a patient in order to treat or prevent graft-versus-host disease, for example, following allogeneic stem cell (*e.g.*, bone marrow) transplantation. Given the large body of evidence to date, it is likely that therapies reducing the expression of IL-17 or otherwise reducing its levels in circulation or target tissues (*e.g.*, anti-IL17 monoclonal antibodies) could have broad applications in the treatment of autoimmune diseases and other inflammatory conditions. In some embodiments, the compounds provided herein may be administered to a patient in order to reduce the expression of IL-17 or its levels in circulation or target tissues (*e.g.*, anti-IL17 monoclonal antibodies). In some embodiments, the compounds provided herein may be administered to a patient in order to treat autoimmune diseases or other inflammatory conditions.

Overproduction of IL-17 or elevated numbers of Th17 cells have been reported in patient studies or animal models of a large number of conditions, including autoimmune diseases, neurological disorders, cardiovascular diseases, cancer, psychiatric and neuropsychiatric disorders, acute and chronic inflammatory conditions, chronic pain syndromes, organ rejection or graft-versus-host disease, or asthma and other allergic conditions. In some embodiments, the compounds provided herein may be administered to a patient in order to treat or prevent one or more of these diseses or disorders.

Both the differentiation of Th17 cells and their production of IL-17 are regulated to a significant degree by the RAR-related orphan receptor RORγt, a member of the nuclear hormone receptor family. Expression of RORγt is common to all types of Th17 cells. RORγ also regulates the production of IL-17 in other cell types, including γδ T cells, innate lymphoid cells, and lymphoid tissue inducer cells (Bronner *et al.*, 2016). Inhibition of RORγt activity results in reduced expression of IL-17. In some embodiments, the compounds provided herein may be administered to a patient in order to inhibit RORγt activity.

Compounds and compositions provided herein may be used to suppress IL-17 production in cultures of human T cells that are exposed to a mixture of cytokines known to induce differentiation into Th17 cells. In some embodiments, the ability to act as inverse agonists of RORγt is also demonstrated. Without wishing to be bound by any theory, it is believed that, for example, RORγt-independent mechanisms appear to contribute to the suppression of IL-17 production. Thus, the compounds and compositions provided herein may be used for inhibiting differentiation of T cells into Th17 cells, as well as inhibiting production of IL-17 by mature Th17 cells. In some of these embodiments, the net result is a reduction in IL-17 levels. In some embodiments, the compounds provided herein may be administered to a patient in order to suppress IL-17 production in one or more of the patient's tissues or organs.

III. Pharmaceutical Formulations and Routes of Administration

For the purpose of administration to a patient in need of such treatment, pharmaceutical formulations (also referred to as a pharmaceutical preparations, pharmaceutical compositions, pharmaceutical products, medicinal products, medicines, medications, or medicaments) comprise a therapeutically effective amount of a compound of the present invention formulated with one or more excipients and/or drug carriers appropriate to the indicated route of administration. In some embodiments, the compounds of the present invention are formulated in a manner amenable for the treatment of human and/or veterinary patients. In some embodiments, formulation comprises admixing or combining one or more of the compounds of the present invention with one or more of the following excipients: lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol. In some embodiments, *e.g.*, for oral administration, the pharmaceutical formulation may be tableted or encapsulated. In some embodiments, the compounds may be dissolved or slurried in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Pharmaceutical formulations may be subjected to conventional pharmaceutical operations, such as sterilization and/or may contain drug carriers and/or excipients such as preservatives, stabilizers, wetting agents, emulsifiers, encapsulating agents such as lipids, dendrimers, polymers, proteins such as albumin, or nucleic acids, and buffers, *etc*.

Pharmaceutical formulations may be administered by a variety of methods, *e.g.*, orally or by injection (*e.g.* subcutaneous, intravenous, intraperitoneal, *etc.*). Depending on the route of administration, the compounds of the present invention may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. To administer the active compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the active compound may be administered to a patient in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes.

The compounds of the present invention may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion

and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

The compounds of the present invention can be administered orally, for example, with an inert diluent or an assimilable edible carrier. The compounds and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds of the present invention may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such pharmaceutical formulations is such that a suitable dosage will be obtained.

The therapeutic compound may also be administered topically to the skin, eye, ear, or mucosal membranes. Administration of the therapeutic compound topically may include formulations of the compounds as a topical solution, lotion, cream, ointment, gel, foam, transdermal patch, or tincture. When the therapeutic compound is formulated for topical administration, the compound may be combined with one or more agents that increase the permeability of the compound through the tissue to which it is administered. In other embodiments, it is contemplated that the topical administration is administered to the eye. Such administration may be applied to the surface of the cornea, conjunctiva, or sclera. Without wishing to be bound by any theory, it is believed that administration to the surface of the eye allows the therapeutic compound to reach the posterior portion of the eye. Ophthalmic topical administration can be formulated as a solution, suspension, ointment, gel, or emulsion. Finally, topical administration may also include administration to the mucosa membranes such as the inside of the mouth. Such administration can be directly to a particular location within the mucosal membrane such as a tooth, a sore, or an ulcer. Alternatively, if local delivery to the lungs is desired the therapeutic compound may be administered by inhalation in a dry-powder or aerosol formulation.

In some embodiments, it may be advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. In some embodiments, the specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of a selected condition in a patient. In some embodiments, active compounds are administered at a therapeutically effective dosage sufficient to treat a condition associated with a condition in a patient. For example, the efficacy of

a compound can be evaluated in an animal model system that may be predictive of efficacy in treating the disease in a human or another animal.

In some embodiments, the effective dose range for the therapeutic compound can be extrapolated from effective doses determined in animal studies for a variety of different animals. In general a human equivalent dose (HED) in mg/kg can be calculated in accordance with the following formula (see, *e.g.*, Reagan-Shaw *et al., FASEB J.,* 22(3):659-661, 2008, which is incorporated herein by reference):

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times (\text{Animal } K_m/\text{Human } K_m)$$

Use of the K_m factors in conversion results in more accurate HED values, which are based on body surface area (BSA) rather than only on body mass. K_m values for humans and various animals are well known. For example, the K_m for an average 60 kg human (with a BSA of 1.6 m^2) is 37, whereas a 20 kg child (BSA 0.8 m^2) would have a K_m of 25. K_m for some relevant animal models are also well known, including: mice K_m of 3 (given a weight of 0.02 kg and BSA of 0.007); hamster K_m of 5 (given a weight of 0.08 kg and BSA of 0.02); rat K_m of 6 (given a weight of 0.15 kg and BSA of 0.025) and monkey K_m of 12 (given a weight of 3 kg and BSA of 0.24).

Precise amounts of the therapeutic composition depend on the judgment of the practitioner and are peculiar to each individual. Nonetheless, a calculated HED dose provides a general guide. Other factors affecting the dose include the physical and clinical state of the patient, the route of administration, the intended goal of treatment and the potency, stability and toxicity of the particular therapeutic formulation.

The actual dosage amount of a compound of the present disclosure or composition comprising a compound of the present disclosure administered to a subject may be determined by physical and physiological factors such as type of animal treated, age, sex, body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the subject and on the route of administration. These factors may be determined by a skilled artisan. The practitioner responsible for administration will typically determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. The dosage may be adjusted by the individual physician in the event of any complication.

In some embodiments, the therapeutically effective amount typically will vary from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 100 mg/kg to about 500 mg/kg, from about 1 mg/kg to about 250 mg/kg, from about 10 mg/kg to about 150 mg/kg in one or more dose administrations daily, for one or several days (depending of course of the mode of administration and the factors discussed above). Other suitable dose ranges include 1 mg to 10,000 mg per day, 100 mg to 10,000 mg per day, 500 mg to 10,000 mg per day, and 500 mg to 1,000 mg per day. In some particular embodiments, the amount is less than 10,000 mg per day with a range of 750 mg to 9,000 mg per day.

In some embodiments, the amount of the active compound in the pharmaceutical formulation is from about 2 to about 75 weight percent. In some of these embodiments, the amount if from about 25 to about 60 weight percent.

Single or multiple doses of the agents are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the agent is administered once a day.

The agent(s) may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks there-between. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months, *etc.* In other embodiments, the invention provides that the agent(s) may taken orally and that the timing of which is or is not dependent upon food intake. Thus, for example, the agent can be taken every morning and/or every evening, regardless of when the subject has eaten or will eat.

IV. Combination Therapy

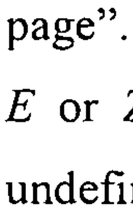
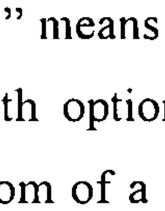
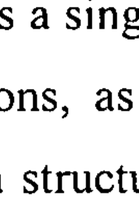
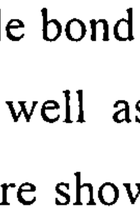
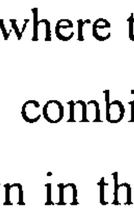
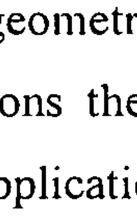
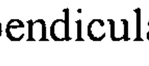
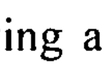
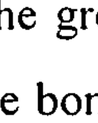
In addition to being used as a monotherapy, the compounds of the present invention may also find use in combination therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, administered at the same time, wherein one composition includes a compound of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

Non-limiting examples of such combination therapy include combination of one or more compounds of the invention with another anti-inflammatory agent, a chemotherapeutic agent, radiation therapy, an antidepressant, an antipsychotic agent, an anticonvulsant, a mood stabilizer, an anti-infective agent, an antihypertensive agent, a cholesterol-lowering agent or other modulator of blood lipids, an agent for promoting weight loss, an antithrombotic agent, an agent for treating or preventing cardiovascular events such as myocardial infarction or stroke, an antidiabetic agent, an agent for reducing transplant rejection or graft-versus-host disease, an anti-arthritic agent, an analgesic agent, an anti-asthmatic agent or other treatment for respiratory diseases, or an agent for treatment or prevention of skin disorders. Compounds of the invention may be combined with agents designed to improve a patient's immune response to cancer, including (but not limited to) cancer vaccines. See Lu *et al.* (2011), which is incorporated herein by reference.

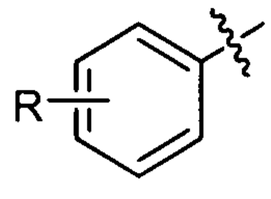
V. Definitions

When used in the context of a chemical group: "hydrogen" means −H; "hydroxy" means −OH; "oxo" means =O; "carbonyl" means −C(=O)−; "carboxy" means −C(=O)OH (also written as −COOH or $-CO_2H$); "halo" means independently −F, −Cl, −Br or −I; "amino" means $-NH_2$; "hydroxyamino" means −NHOH; "nitro" means $-NO_2$; imino means =NH; "cyano" means −CN; "isocyanate" means −N=C=O;

"azido" means $-N_3$; in a monovalent context "phosphate" means $-OP(O)(OH)_2$ or a deprotonated form thereof; in a divalent context "phosphate" means $-OP(O)(OH)O-$ or a deprotonated form thereof; "mercapto" means –SH; and "thio" means =S; "sulfonyl" means $-S(O)_2-$; and "sulfinyl" means $-S(O)-$.

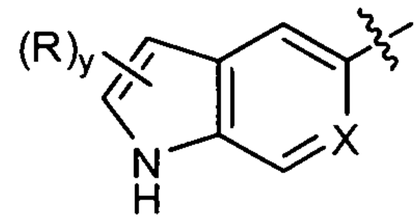
In the context of chemical formulas, the symbol "–" means a single bond, "=" means a double bond, and "≡" means triple bond. The symbol "----" represents an optional bond, which if present is either single or double. The symbol "═══" represents a single bond or a double bond. Thus, the formula  covers, for example,  ,  ,  ,  and  . And it is understood that no one such ring atom forms part of more than one double bond. Furthermore, it is noted that the covalent bond symbol "–", when connecting one or two stereogenic atoms, does not indicate any preferred stereochemistry. Instead, it covers all stereoisomers as well as mixtures thereof. The symbol "  ", when drawn perpendicularly across a bond (*e.g.*,  for methyl) indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups in order to assist the reader in unambiguously identifying a point of attachment. The symbol "  " means a single bond where the group attached to the thick end of the wedge is "out of the page." The symbol "" means a single bond where the group attached to the thick end of the wedge is "into the page". The symbol "  " means a single bond where the geometry around a double bond (*e.g.*, either *E* or *Z*) is undefined. Both options, as well as combinations thereof are therefore intended. Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to that atom. A bold dot on a carbon atom indicates that the hydrogen attached to that carbon is oriented out of the plane of the paper.

When a variable is depicted as a "floating group" on a ring system, for example, the group "R" in the formula:



,

then the variable may replace any hydrogen atom attached to any of the ring atoms, including a depicted, implied, or expressly defined hydrogen, so long as a stable structure is formed. When a variable is depicted as a "floating group" on a fused ring system, as for example the group "R" in the formula:



,

then the variable may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (*e.g.*, the hydrogen attached to the nitrogen in the formula above), implied hydrogens (*e.g.*, a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (*e.g.*, a hydrogen attached to group X, when X

equals −CH−), so long as a stable structure is formed. In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter "y" immediately following the R enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

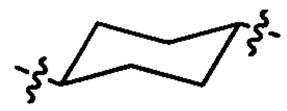
For the chemical groups and compound classes, the number of carbon atoms in the group or class is as indicated as follows: "Cn" defines the exact number (n) of carbon atoms in the group/class. "C≤n" defines the maximum number (n) of carbon atoms that can be in the group/class, with the minimum number as small as possible for the group/class in question. For example, it is understood that the minimum number of carbon atoms in the groups "alkyl$_{(C\leq 8)}$", "alkanediyl$_{(C\leq 8)}$", "heteroaryl$_{(C\leq 8)}$", "acyl$_{(C\leq 8)}$", and "heterocycloalkyl$_{(C\leq 8)}$" is one, the minimum number of carbon atoms in the groups "alkenyl$_{(C\leq 8)}$", "alkenediyl$_{(C\leq 8)}$", and "alkynyl$_{(C\leq 8)}$", is two, the minimum number of carbon atoms in the group "cycloalkyl$_{(C\leq 8)}$" and "cycloalkanediyl$_{(C\leq 8)}$" is three, and the minimum number of carbon atoms in the groups "aryl$_{(C\leq 8)}$" and "arenediyl$_{(C\leq 8)}$" is six. "Cn-n'" defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Thus, "alkyl$_{(C2\text{-}10)}$" designates those alkyl groups having from 2 to 10 carbon atoms. These carbon number indicators may precede or follow the chemical groups or class it modifies and it may or may not be enclosed in parenthesis, without signifying any change in meaning. Thus, the terms "C5 olefin", "C5-olefin", "olefin$_{(C5)}$", and "olefin$_{C5}$" are all synonymous. When any of the chemical groups or compound classes defined herein is modified by the term "substituted", any carbon atom in the moiety replacing the hydrogen atom is not counted. Thus methoxyhexyl, which has a total of seven carbon atoms, is an example of a substituted alkyl$_{(C1\text{-}6)}$. Unless specified otherwise, any chemical group or compound class listed in a claim set without a carbon atom limit has a carbon atom limit of less than or equal to twelve.

The term "saturated" when used to modify a compound or chemical group means the compound or chemical group has no carbon-carbon double and no carbon-carbon triple bonds, except as noted below. When the term is used to modify an atom, it means that the atom is not part of any double or triple bond. In the case of substituted versions of saturated groups, one or more carbon oxygen double bond or a carbon nitrogen double bond may be present. And when such a bond is present, then carbon-carbon double bonds that may occur as part of keto-enol tautomerism or imine/enamine tautomerism are not precluded. When the term "saturated" is used to modify a solution of a substance, it means that no more of that substance can dissolve in that solution.

The term "aliphatic" signifies that the compound or chemical group so modified is an acyclic or cyclic, but non-aromatic compound or group. In aliphatic compounds/groups, the carbon atoms can be joined together in straight chains, branched chains, or non-aromatic rings (alicyclic). Aliphatic compounds/groups can be saturated, that is joined by single carbon-carbon bonds (alkanes/alkyl), or unsaturated, with one or more carbon-carbon double bonds (alkenes/alkenyl) or with one or more carbon-carbon triple bonds (alkynes/alkynyl).

The term "aromatic" signifies that the compound or chemical group so modified hasa planar unsaturated ring of atoms with $4n$ +2 electrons in a fully conjugated cyclic π system.

The term "alkyl" when used without the "substituted" modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, a linear or branched acyclic structure, and no atoms other than carbon and hydrogen. The groups $-CH_3$ (Me), $-CH_2CH_3$ (Et), $-CH_2CH_2CH_3$ (*n*-Pr or propyl), $-CH(CH_3)_2$ (*i*-Pr, ^{i}Pr or isopropyl), $-CH_2CH_2CH_2CH_3$ (*n*-Bu), $-CH(CH_3)CH_2CH_3$ (*sec*-butyl), $-CH_2CH(CH_3)_2$ (isobutyl), $-C(CH_3)_3$ (*tert*-butyl, *t*-butyl, *t*-Bu or ^{t}Bu), and $-CH_2C(CH_3)_3$ (*neo*-pentyl) are non-limiting examples of alkyl groups. The term "alkanediyl" when used without the "substituted" modifier refers to a divalent saturated aliphatic group, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups $-CH_2-$ (methylene), $-CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, and $-CH_2CH_2CH_2-$ are non-limiting examples of alkanediyl groups. The term "alkylidene" when used without the "substituted" modifier refers to the divalent group =CRR′ in which R and R′ are independently hydrogen or alkyl. Non-limiting examples of alkylidene groups include: $=CH_2$, $=CH(CH_2CH_3)$, and $=C(CH_3)_2$. An "alkane" refers to the class of compounds having the formula H–R, wherein R is alkyl as this term is defined above. When any of these terms is used with the "substituted" modifier, one or more hydrogen atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-C(O)H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$. The following groups are non-limiting examples of substituted alkyl groups: $-CH_2OH$, $-CH_2Cl$, $-CF_3$, $-CH_2CN$, $-CH_2C(O)OH$, $-CH_2C(O)OCH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)CH_3$, $-CH_2OCH_3$, $-CH_2OC(O)CH_3$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$, and $-CH_2CH_2Cl$. The term "haloalkyl" is a subset of substituted alkyl, in which the hydrogen atom replacement is limited to halo (*i.e.* $-F$, $-Cl$, $-Br$, or $-I$) such that no other atoms aside from carbon, hydrogen and halogen are present. The group, $-CH_2Cl$ is a non-limiting example of a haloalkyl. The term "fluoroalkyl" is a subset of substituted alkyl, in which the hydrogen atom replacement is limited to fluoro such that no other atoms aside from carbon, hydrogen and fluorine are present. The groups $-CH_2F$, $-CF_3$, and $-CH_2CF_3$ are non-limiting examples of fluoroalkyl groups.

The term "cycloalkyl" when used without the "substituted" modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, said carbon atom forming part of one or more non-aromatic ring structures, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples include: $-CH(CH_2)_2$ (cyclopropyl), cyclobutyl, cyclopentyl, or cyclohexyl (Cy). As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to a carbon atom of the non-aromatic ring structure. The term "cycloalkanediyl" when used without the "substituted" modifier refers to a divalent saturated aliphatic group with two carbon atoms as points of attachment, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The group  is a non-limiting

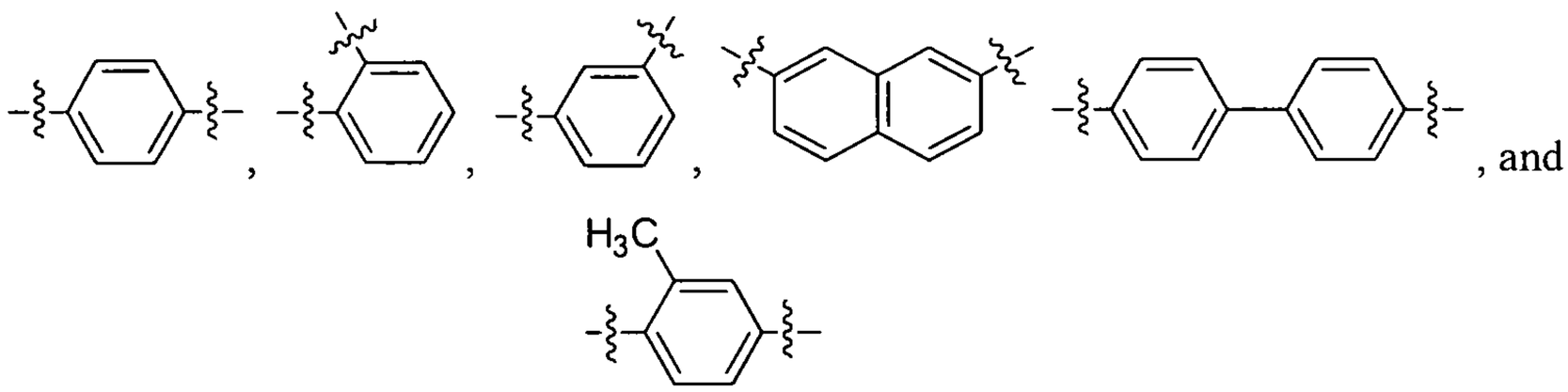
example of cycloalkanediyl group. A "cycloalkane" refers to the class of compounds having the formula H–R, wherein R is cycloalkyl as this term is defined above. When any of these terms is used with the "substituted" modifier, one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, $–NH_2$, $–NO_2$, $–CO_2H$, –C(O)H, $–CO_2CH_3$, –CN, –SH, $–OCH_3$, $–OCH_2CH_3$, $–C(O)CH_3$, $–NHCH_3$, $–NHCH_2CH_3$, $–N(CH_3)_2$, $–C(O)NH_2$, $–C(O)NHCH_3$, $–C(O)N(CH_3)_2$, $–OC(O)CH_3$, $–NHC(O)CH_3$, $–S(O)_2CH_3$, $–S(O)_2OH$, or $–S(O)_2NH_2$.

The term "alkenyl" when used without the "substituted" modifier refers to a monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples include: $–CH=CH_2$ (vinyl), $–CH=CHCH_3$, $–CH=CHCH_2CH_3$, $–CH_2CH=CH_2$ (allyl), $–CH_2CH=CHCH_3$, and $–CH=CHCH=CH_2$. The term "alkenediyl" when used without the "substituted" modifier refers to a divalent unsaturated aliphatic group, with two carbon atoms as points of attachment, a linear or branched, a linear or branched acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. The groups –CH=CH–, $–CH=C(CH_3)CH_2–$, $–CH=CHCH_2–$, and $–CH_2CH=CHCH_2–$ are non-limiting examples of alkenediyl groups. It is noted that while the alkenediyl group is aliphatic, once connected at both ends, this group is not precluded from forming part of an aromatic structure. The terms "alkene" and "olefin" are synonymous and refer to the class of compounds having the formula H–R, wherein R is alkenyl as this term is defined above. Similarly, the terms "terminal alkene" and "α-olefin" are synonymous and refer to an alkene having just one carbon-carbon double bond, wherein that bond is part of a vinyl group at an end of the molecule. When any of these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, $–NH_2$, $–NO_2$, $–CO_2H$, –C(O)H, $–CO_2CH_3$, –CN, –SH, $–OCH_3$, $–OCH_2CH_3$, $–C(O)CH_3$, $–NHCH_3$, $–NHCH_2CH_3$, $–N(CH_3)_2$, $–C(O)NH_2$, $–C(O)NHCH_3$, $–C(O)N(CH_3)_2$, $–OC(O)CH_3$, $–NHC(O)CH_3$, $–S(O)_2CH_3$, $–S(O)_2OH$, or $–S(O)_2NH_2$. The groups –CH=CHF, –CH=CHCl and –CH=CHBr are non-limiting examples of substituted alkenyl groups.

The term "alkynyl" when used without the "substituted" modifier refers to a monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. As used herein, the term alkynyl does not preclude the presence of one or more non-aromatic carbon-carbon double bonds. The groups $–C≡CH$, $–C≡CCH_3$, and $–CH_2C≡CCH_3$ are non-limiting examples of alkynyl groups. An "alkyne" refers to the class of compounds having the formula H–R, wherein R is alkynyl. When any of these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, $–NH_2$, $–NO_2$, $–CO_2H$, –C(O)H, $–CO_2CH_3$, –CN, –SH, $–OCH_3$, $–OCH_2CH_3$, $–C(O)CH_3$, $–NHCH_3$, $–NHCH_2CH_3$, $–N(CH_3)_2$, $–C(O)NH_2$, $–C(O)NHCH_3$, $–C(O)N(CH_3)_2$, $–OC(O)CH_3$, $–NHC(O)CH_3$, $–S(O)_2CH_3$, $–S(O)_2OH$, or $–S(O)_2NH_2$.

The term "aryl" when used without the "substituted" modifier refers to a monovalent unsaturated aromatic group with an aromatic carbon atom as the point of attachment, said carbon atom forming part

of a one or more aromatic ring structures, each with six ring atoms that are all carbon, and wherein the group consists of no atoms other than carbon and hydrogen. If more than one ring is present, the rings may be fused or unfused. Unfused rings are connected with a covalent bond. As used herein, the term aryl does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, $-C_6H_4CH_2CH_3$ (ethylphenyl), naphthyl, and a monovalent group derived from biphenyl (*e.g.*, 4-phenylphenyl). The term "arenediyl" when used without the "substituted" modifier refers to a divalent aromatic group with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structures, each with six ring atoms that are all carbon, and wherein the divalent group consists of no atoms other than carbon and hydrogen. As used herein, the term arenediyl does not preclude the presence of one or more alkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. If more than one ring is present, the rings may be fused or unfused. Unfused rings are connected with a covalent bond. Non-limiting examples of arenediyl groups include:



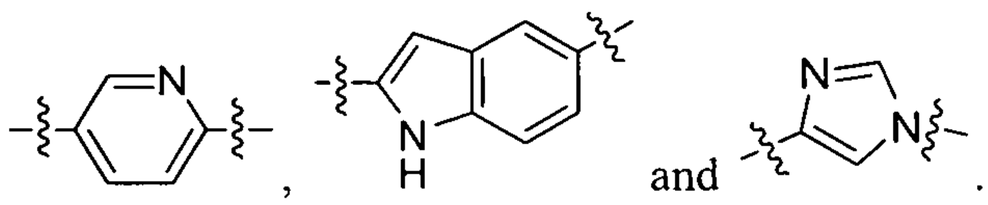
, and

An "arene" refers to the class of compounds having the formula H–R, wherein R is aryl as that term is defined above. Benzene and toluene are non-limiting examples of arenes. When any of these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-C(O)H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$.

The term "aralkyl" when used without the "substituted" modifier refers to the monovalent group –alkanediyl–aryl, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples are: phenylmethyl (benzyl, Bn) and 2-phenyl-ethyl. When the term aralkyl is used with the "substituted" modifier one or more hydrogen atom from the alkanediyl and/or the aryl group has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-C(O)H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, and 2-chloro-2-phenyl-eth-1-yl.

The term "heteroaryl" when used without the "substituted" modifier refers to a monovalent aromatic group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more aromatic ring structures, each ring structure having

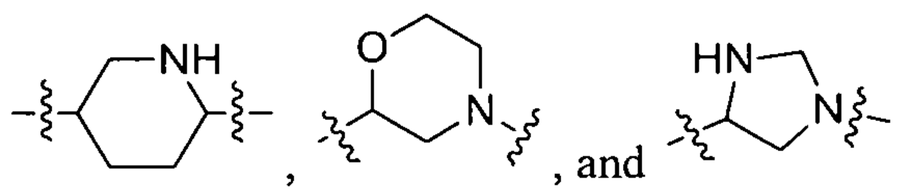
three to eight ring atoms, wherein at least one of the ring atoms of the aromatic ring structure(s) is nitrogen, oxygen or sulfur, and wherein the heteroaryl group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings are fused; however, the term heteroaryl does not preclude the presence of one or more alkyl, cycloalkyl, heterocycloalkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to one or more ring atoms. Non-limiting examples of heteroaryl groups include furanyl, imidazolyl, indolyl, indazolyl (Im), isoxazolyl, methylpyridinyl, oxazolyl, phenylpyridinyl, pyridinyl (pyridyl), pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, triazinyl, tetrazolyl, thiazolyl, thienyl, and triazolyl. The term "heteroarenediyl" when used without the "substituted" modifier refers to a divalent aromatic group, with two aromatic carbon atoms, two aromatic nitrogen atoms, or one aromatic carbon atom and one aromatic nitrogen atom as the two points of attachment, said atoms forming part of one or more aromatic ring structures, each with three to eight ring atoms, wherein at least one of the ring atoms of the aromatic ring structure(s) is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings are be fused; however, the term heteroarenediyl does not preclude the presence of one or more alkyl or aryl groups (carbon number limitation permitting) attached to one or more ring atoms. Non-limiting examples of heteroarenediyl groups include:



The term "*N*-heteroaryl" refers to a heteroaryl group with a nitrogen atom as the point of attachment. A "heteroarene" refers to the class of compounds having the formula H−R, wherein R is heteroaryl. Pyridine and quinoline are non-limiting examples of heteroarenes. When these terms are used with the "substituted" modifier one or more hydrogen atom on either the heteroaryl ring or any alkyl, cycloalkyl, heterocycloalkyl, aryl, and/or aralkyl groups attached thereto has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, −C(O)H, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$.

The term "heterocycloalkyl" when used without the "substituted" modifier refers to a monovalent non-aromatic group with a carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more non-aromatic ring structures, each ring structure having three to eight ring atoms, wherein at least one of the ring atoms of the non-aromatic ring structure(s) is nitrogen, oxygen or sulfur, and wherein the heterocycloalkyl group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. If more than one ring is present, the rings are fused. As used herein, the term does not preclude the presence of one or more alkyl or cycloalkyl groups (carbon number limitation permitting) attached to one or more ring atoms. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkyl groups include aziridinyl, azetidinyl,

pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, pyranyl, oxiranyl, and oxetanyl. The term "heterocycloalkanediyl" when used without the "substituted" modifier refers to a divalent cyclic group, with two carbon atoms, two nitrogen atoms, or one carbon atom and one nitrogen atom as the two points of attachment, said atoms forming part of one or more ring structure(s) wherein at least one of the ring atoms of the non-aromatic ring structure(s) is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. If more than one ring is present, the rings are fused. As used herein, the term heterocycloalkanediyl does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to one or more ring atoms. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkanediyl groups include:



, , and .

The term "*N*-heterocycloalkyl" refers to a heterocycloalkyl group with a nitrogen atom as the point of attachment. *N*-pyrrolidinyl is an example of such a group. When these terms are used with the "substituted" modifier one or more hydrogen atom on either the heterocycloalkyl ring or any alkyl and/or cycloalkyl groups attached thereto has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-C(O)H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$.

The term "acyl" when used without the "substituted" modifier refers to the group $-C(O)R$, in which R is a hydrogen, alkyl, cycloalkyl, or aryl as those terms are defined above. The groups, $-CHO$, $-C(O)CH_3$ (acetyl, Ac), $-C(O)CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-C(O)CH(CH_2)_2$, $-C(O)C_6H_5$, and $-C(O)C_6H_4CH_3$ are non-limiting examples of acyl groups. A "thioacyl" is defined in an analogous manner, except that the oxygen atom of the group $-C(O)R$ has been replaced with a sulfur atom, $-C(S)R$. The term "aldehyde" corresponds to an alkyl group, as defined above, attached to a $-CHO$ group. When any of these terms are used with the "substituted" modifier one or more hydrogen atom (including a hydrogen atom directly attached to the carbon atom of the carbonyl or thiocarbonyl group, if any) has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-C(O)H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$. The groups, $-C(O)CH_2CF_3$, $-CO_2H$ (carboxyl), $-CO_2CH_3$ (methylcarboxyl), $-CO_2CH_2CH_3$, $-C(O)NH_2$ (carbamoyl), and $-CON(CH_3)_2$, are non-limiting examples of substituted acyl groups.

The term "alkoxy" when used without the "substituted" modifier refers to the group $-OR$, in which R is an alkyl, as that term is defined above. Non-limiting examples include: $-OCH_3$ (methoxy), $-OCH_2CH_3$ (ethoxy), $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$ (isopropoxy), or $-OC(CH_3)_3$ (*tert*-butoxy). The terms "cycloalkoxy", "alkenyloxy", "alkynyloxy", "aryloxy", "aralkoxy", "heteroaryloxy",

"heterocycloalkoxy", and "acyloxy", when used without the "substituted" modifier, refers to groups, defined as −OR, in which R is cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and acyl, respectively. The term "alkylthio" and "acylthio" when used without the "substituted" modifier refers to the group −SR, in which R is an alkyl and acyl, respectively. The term "alcohol" corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a hydroxy group. The term "ether" corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with an alkoxy group. When any of these terms is used with the "substituted" modifier, one or more hydrogen atom has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, −C(O)H, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$.

The term "alkylamino" when used without the "substituted" modifier refers to the group −NHR, in which R is an alkyl, as that term is defined above. Non-limiting examples include: $-NHCH_3$ and $-NHCH_2CH_3$. The term "dialkylamino" when used without the "substituted" modifier refers to the group −NRR′, in which R and R′ can be the same or different alkyl groups. Non-limiting examples of dialkylamino groups include: $-N(CH_3)_2$ and $-N(CH_3)(CH_2CH_3)$. The terms "cycloalkylamino", "alkenylamino", "alkynylamino", "arylamino", "aralkylamino", "heteroarylamino", "heterocycloalkylamino", and "alkoxyamino" when used without the "substituted" modifier, refers to groups, defined as −NHR, in which R is cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and alkoxy, respectively. A non-limiting example of an arylamino group is $-NHC_6H_5$. The term "amido" (acylamino), when used without the "substituted" modifier, refers to the group −NHR, in which R is acyl, as that term is defined above. A non-limiting example of an amido group is $-NHC(O)CH_3$. When any of these terms is used with the "substituted" modifier, one or more hydrogen atom attached to a carbon atom has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, −C(O)H, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$. The groups $-NHC(O)OCH_3$ and $-NHC(O)NHCH_3$ are non-limiting examples of substituted amido groups.

The use of the word "a" or "an," when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects.

An "active ingredient" (AI) (also referred to as an active compound, active substance, active agent, pharmaceutical agent, agent, biologically active molecule, or a therapeutic compound) is the ingredient in a pharmaceutical drug or a pesticide that is biologically active. The similar terms active

pharmaceutical ingredient (API) and bulk active are also used in medicine, and the term active substance may be used for pesticide formulations.

The terms "comprise," "have" and "include" are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as "comprises," "comprising," "has," "having," "includes" and "including," are also open-ended. For example, any method that "comprises," "has" or "includes" one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

The term "effective," as that term is used in the specification and/or claims, means adequate to accomplish a desired, expected, or intended result. "Effective amount," "Therapeutically effective amount" or "pharmaceutically effective amount" when used in the context of treating a patient or subject with a compound means that amount of the compound which, when administered to a subject or patient for treating or preventing a disease, is an amount sufficient to effect such treatment or prevention of the disease.

An "excipient" is a pharmaceutically acceptable substance formulated along with the active ingredient(s) of a medication, pharmaceutical composition, formulation, or drug delivery system. Excipients may be used, for example, to stabilize the composition, to bulk up the composition (thus often referred to as "bulking agents," "fillers," or "diluents" when used for this purpose), or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption, reducing viscosity, or enhancing solubility. Excipients include pharmaceutically acceptable versions of antiadherents, binders, coatings, colors, disintegrants, flavors, glidants, lubricants, preservatives, sorbents, sweeteners, and vehicles. The main excipient that serves as a medium for conveying the active ingredient is usually called the vehicle. Excipients may also be used in the manufacturing process, for example, to aid in the handling of the active substance, such as by facilitating powder flowability or non-stick properties, in addition to aiding *in vitro* stability such as prevention of denaturation or aggregation over the expected shelf life. The suitability of an excipient will typically vary depending on the route of administration, the dosage form, the active ingredient, as well as other factors.

The term "hydrate" when used as a modifier to a compound means that the compound has less than one (*e.g.*, hemihydrate), one (*e.g.*, monohydrate), or more than one (*e.g.*, dihydrate) water molecules associated with each compound molecule, such as in solid forms of the compound.

As used herein, the term "IC_{50}" refers to an inhibitory dose which is 50% of the maximum response obtained. This quantitative measure indicates how much of a particular drug or other substance (inhibitor) is needed to inhibit a given biological, biochemical or chemical process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half.

An "isomer" of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term "patient" or "subject" refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In

certain embodiments, the patient or subject is a primate. Non-limiting examples of human patients are adults, juveniles, infants and fetuses.

As generally used herein "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4′-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, *o*-(4-hydroxybenzoyl)benzoic acid, oxalic acid, *p*-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, *p*-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (P. H. Stahl & C. G. Wermuth eds., Verlag Helvetica Chimica Acta, 2002).

A "pharmaceutically acceptable carrier," "drug carrier," or simply "carrier" is a pharmaceutically acceptable substance formulated along with the active ingredient medication that is involved in carrying, delivering and/or transporting a chemical agent. Drug carriers may be used to improve the delivery and the effectiveness of drugs, including for example, controlled-release technology to modulate drug bioavailability, decrease drug metabolism, and/or reduce drug toxicity. Some drug carriers may increase the effectiveness of drug delivery to the specific target sites. Examples of carriers include: liposomes, microspheres (*e.g.*, made of poly(lactic-co-glycolic) acid), albumin microspheres, synthetic polymers, nanofibers, protein-DNA complexes, protein conjugates, erythrocytes, virosomes, and dendrimers.

A "pharmaceutical drug" (also referred to as a pharmaceutical, pharmaceutical preparation, pharmaceutical composition, pharmaceutical formulation, pharmaceutical product, medicinal product, medicine, medication, medicament, or simply a drug) is a compound or composition used to diagnose, cure, treat, or prevent disease. An active ingredient (AI) (defined above) is the ingredient in a pharmaceutical drug or a pesticide that is biologically active. The similar terms active pharmaceutical ingredient (API) and bulk active are also used in medicine, and the term active substance may be used for pesticide formulations. Some medications and pesticide products may contain more than one active ingredient. In contrast with the active ingredients, the inactive ingredients are usually called excipients (defined above) in pharmaceutical contexts.

"Prevention" or "preventing" includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

"Prodrug" means a compound that is convertible *in vivo* metabolically into an inhibitor according to the present invention. The prodrug itself may or may not also have activity with respect to a given target protein. For example, a compound comprising a hydroxy group may be administered as an ester that is converted by hydrolysis *in vivo* to the hydroxy compound. Suitable esters that may be converted *in vivo* into hydroxy compounds include acetates, citrates, lactates, phosphates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoate, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, *p*-toluenesulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like. Similarly, a compound comprising an amine group may be administered as an amide that is converted by hydrolysis *in vivo* to the amine compound.

A "stereoisomer" or "optical isomer" is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers. Chiral molecules contain a chiral center, also referred to as a stereocenter or stereogenic center, which is any point, though not necessarily an atom, in a molecule bearing groups such that an interchanging of any two groups leads to a stereoisomer. In organic compounds, the chiral center is typically a carbon, phosphorus or sulfur atom, though it is also possible for other atoms to be stereocenters in organic and inorganic compounds. A molecule can have multiple stereocenters, giving it many stereoisomers. In compounds whose stereoisomerism is due to tetrahedral stereogenic centers (*e.g.*, tetrahedral carbon), the total number of hypothetically possible stereoisomers will not exceed 2^n, where n is the number of tetrahedral stereocenters. Molecules with symmetry frequently have fewer than the maximum possible number of stereoisomers. A 50:50 mixture of enantiomers is referred to as a racemic mixture.

Alternatively, a mixture of enantiomers can be enantiomerically enriched so that one enantiomer is present in an amount greater than 50%. Typically, enantiomers and/or diastereomers can be resolved or separated using techniques known in the art. It is contemplated that that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its *R* form, *S* form, or as a mixture of the *R* and *S* forms, including racemic and non-racemic mixtures. As used herein, the phrase "substantially free from other stereoisomers" means that the composition contains ≤ 15%, more preferably ≤ 10%, even more preferably ≤ 5%, or most preferably ≤ 1% of another stereoisomer(s).

"Treatment" or "treating" includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (*e.g.*, reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a disease or symptom(s) in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

The term "unit dose" refers to a formulation of the compound or composition such that the formulation is prepared in a manner sufficient to provide a single therapeutically effective dose of the active ingredient to a patient in a single administration. Such unit dose formulations that may be used include but are not limited to a single tablet, capsule, or other oral formulations, or a single vial with a syringable liquid or other injectable formulations.

Other abbreviations used herein are as follows: NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; FBS, fetal bovine serum; IFNγ or IFN-γ, interferon-γ; TNFα or TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL17 or IL-17, interleukin 17; RORγ, retinoic acid receptor-related orphan receptor γ; HO-1, inducible heme oxygenase; Me, methyl; Bn, benzyl; Et, ethyl; Pr, propyl; *i*Pr, isopropyl; Bu, butyl; *i*-Bu, isobutyl; *t*Bu or Bu^t, *tert*-butyl; Ph, phenyl; Ac, acetyl; Bz, benzoyl; Ts, tosyl; Boc, *t*-butyloxycarbonyl; quant., quantitative; aq., aqueous; w/w, weight per weight; °C, degrees Celsius, N, normal or normality; h or hr, hours; atm, atmosphere; rt, room temperature; TLC, thin layer chromatography; DMSO, dimethyl sulfoxide; EtOAc, ethyl acetate; DMF, *N,N*-dimethylformamide; DMA, dimethylacetamide; MeCN, acetonitrile; MTBE, methyl *t*-butylether; Et_2O, diethyl ether; THF, tetrahydrofuran; MeOH, methanol, EtOH, ethanol; *i*PrOH, isopropanol; HMPA, hexamethylphosphoramide; DME, dimethoxyethane; Pd/C, palladium on carbon; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium(0); $Pd(dppf)Cl_2$, [1,1′-bis(diphenylphosphino)ferrocene]dichloro-palladium(II); Ac_2O, acetic anhydride; Tf_2O, trifluoromethanesulfonic anhydride; MsCl, mesyl choloride; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TsOH or *p*-TsOH, *p*-toluenesulfonic acid; Py, pyridine; Et_3N, triethylamine; LDA, lithium diisopropylamide; DIPEA, diisopropylethylamine; LHMDS, lithium bis(trimethylsilyl)amide; DMAP, dimethylaminopyridine; NMP, *N*-methyl-2-pyrrolidone; mCPBA or *m*-CPBA, *m*-chloroperoxybenzoic acid; MOMCl, methoxymethyl chloride; TBSCl, *t*-butyldimethylsilyl chloride; SEMCl, 2-(trimethylsilyl)ethoxymethyl chloride; TBAF, tetra-*n*-butylammonium fluoride; PDC, pyridinium dichromate; DMP, Dess Martin periodinane; IBX, 2-

iodoxybenzoic acid; T_3P®, propylphosphonic anhydride; DPPA, diphenylphosphoryl azide; Ph_3P or PPh_3, triphenyl phosphine; HATU, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; NMO, *N*-methylmorpholine *N*-oxide; Xphos, 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; Xantphos, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; PPTS, pyridinium *p*-toluenesulfonate; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DAST, diethylaminosulfur trifluoride; $TMSCHN_2$, trimethylsilyldiazomethane; 9-BBN, 9-borabicyclo-[3.3.1]nonane; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin.

The above definitions supersede any conflicting definition in any reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present invention.

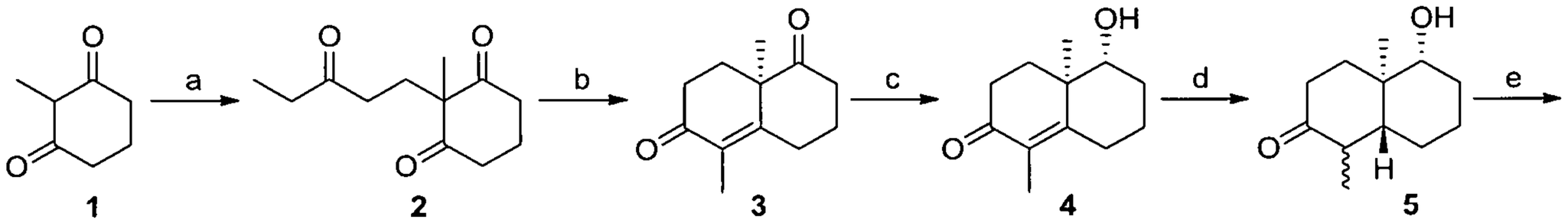
VI. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1: Synthesis and Characterization

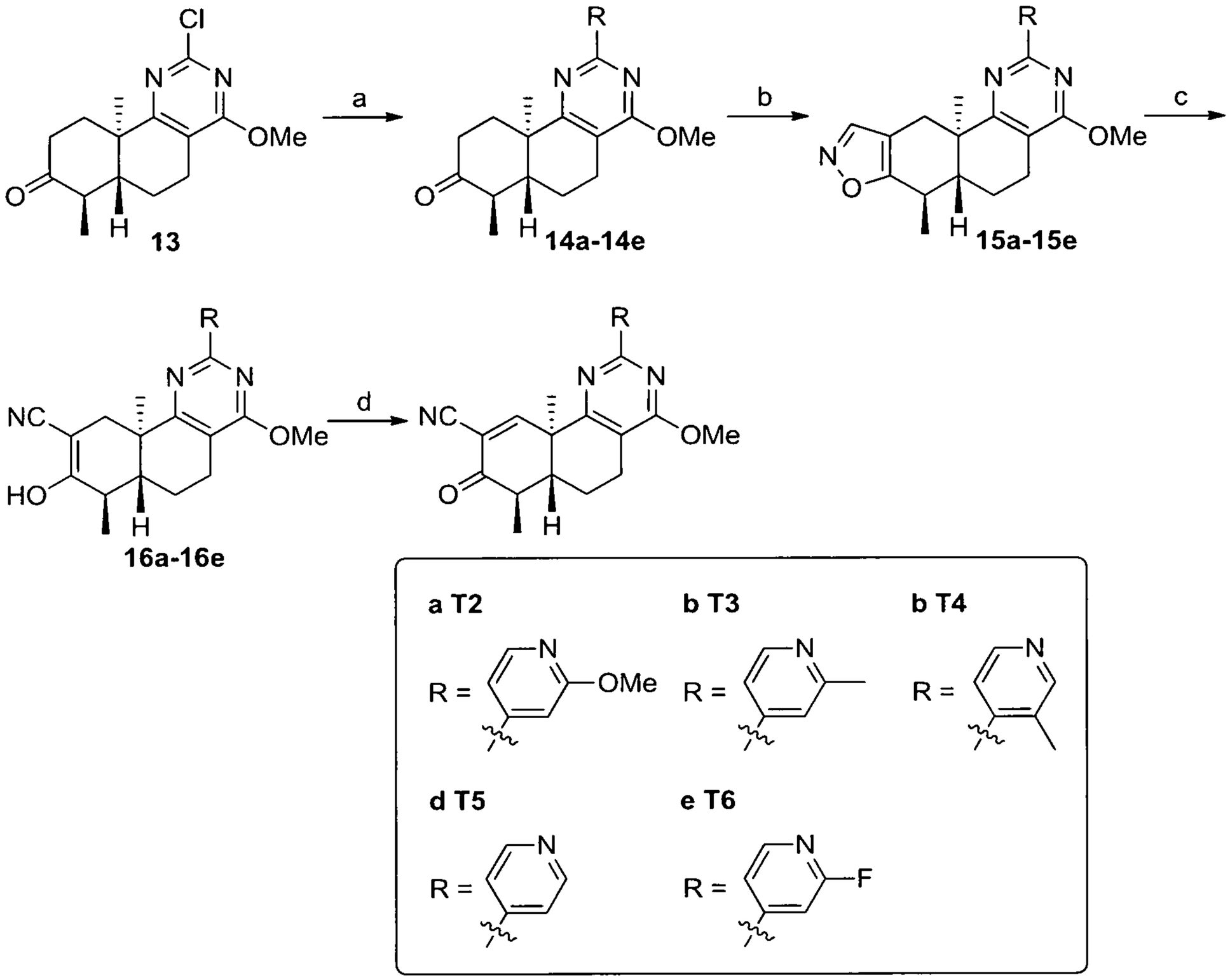
i. Synthesis

Scheme 1



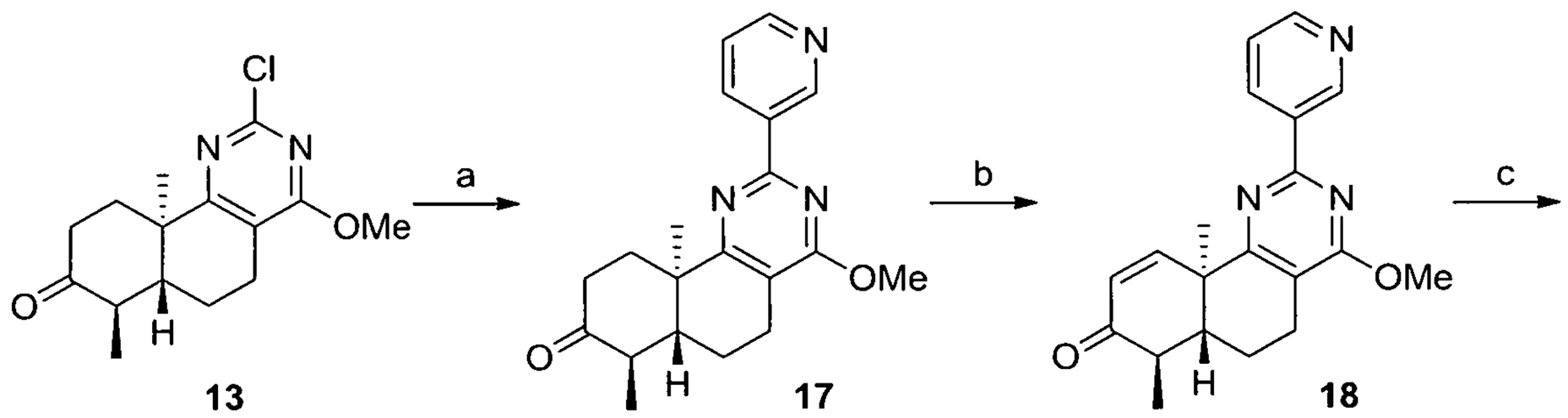
Reagents and conditions: a) Ethyl vinyl ketone, Et_3N, MeCN, rt; b) i) (*R*)-phenylalanine, (1*S*)-(+)-camphorsulfonic acid, MeCN, 50 - 60 °C; ii) crystallization; c) $NaBH_4$, EtOH, -5 °C; d) H_2, 5% $Pd/BaSO_4$, EtOAc, 20 °C; e) aq. 3 N HCl, EtOH, 20 °C; f) ethylene glycol, PPTS, toluene, reflux, $-H_2O$; g) $Na_2WO_4 \cdot 2H_2O$, $Na_2HPO_4 \cdot 12H_2O$, aq. 30% H_2O_2, DMA, 90 °C; h) $CO(OMe)_2$, NaH, THF, rt-80 °C; i) thiourea, $KOBu^t$, EtOH, reflux; j) $ClCH_2CO_2H$, H_2O, conc. HCl, 75-100 °C; k) $POCl_3$, DIPEA, 90 °C; l) NaOMe, MeOH, 50 °C.

Scheme 2



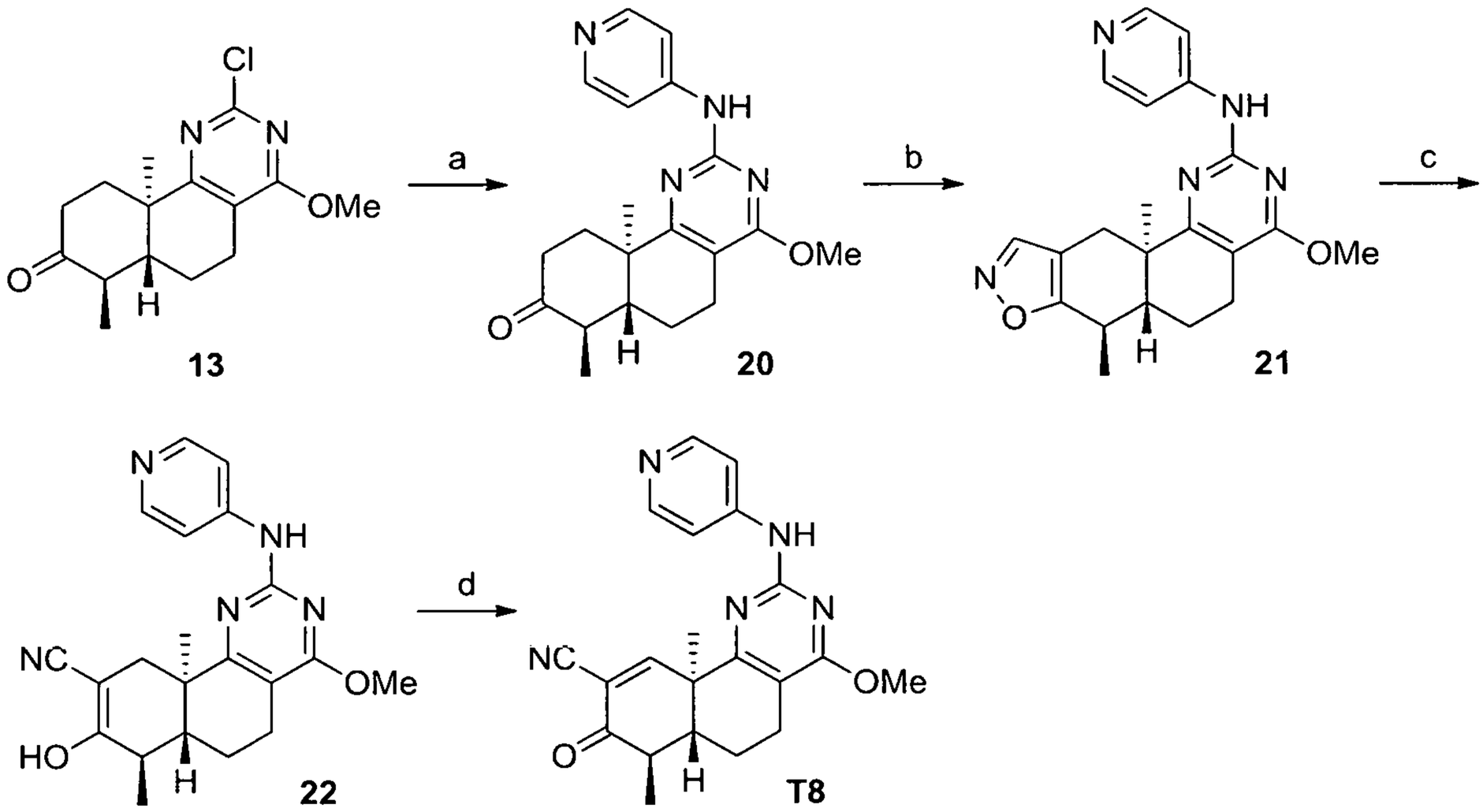
Reagents and conditions: a) boronic acid or boronic ester, Ph_3P, K_3PO_4, $Pd(OAc)_2$, DME, DMF; b) i) HCO_2Et, NaOMe, MeOH, rt; ii) $NH_2OH \cdot HCl$, EtOH, H_2O, 55 °C; c) NaOMe, MeOH, 55 °C; or K_2CO_3, MeOH, rt; e) DDQ, benzene, reflux.

Scheme 3



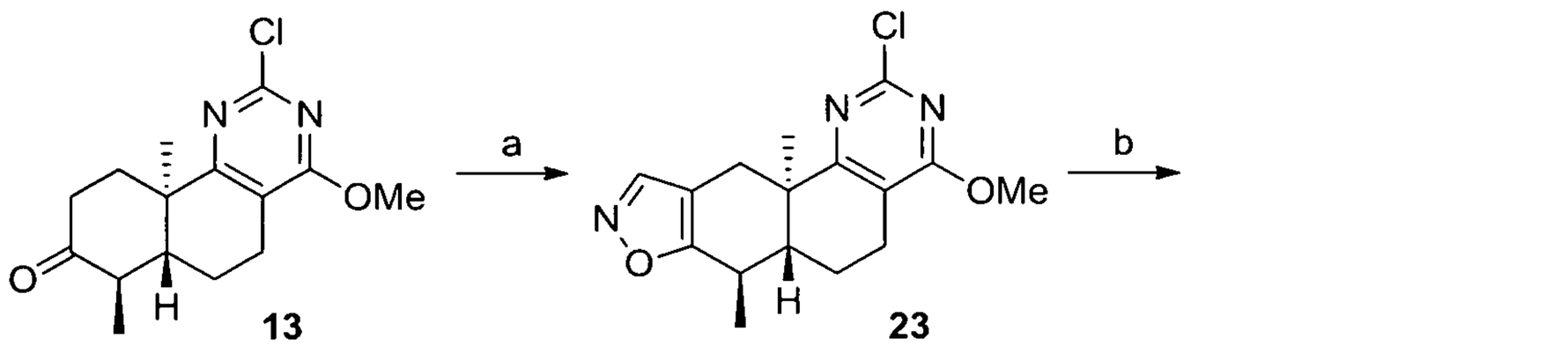
Reagents and conditions: a) pyridine-3-boronic acid, Ph_3P, K_3PO_4, $Pd(OAc)_2$, DME, DMF, microwave, 100 °C; b) i) LHMDS, PhSeCl, THF, -78 °C; ii) 30% aq. H_2O_2, EtOAc, THF, rt; c) I_2, pyridine, 80 °C; d) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80 °C.

Scheme 4



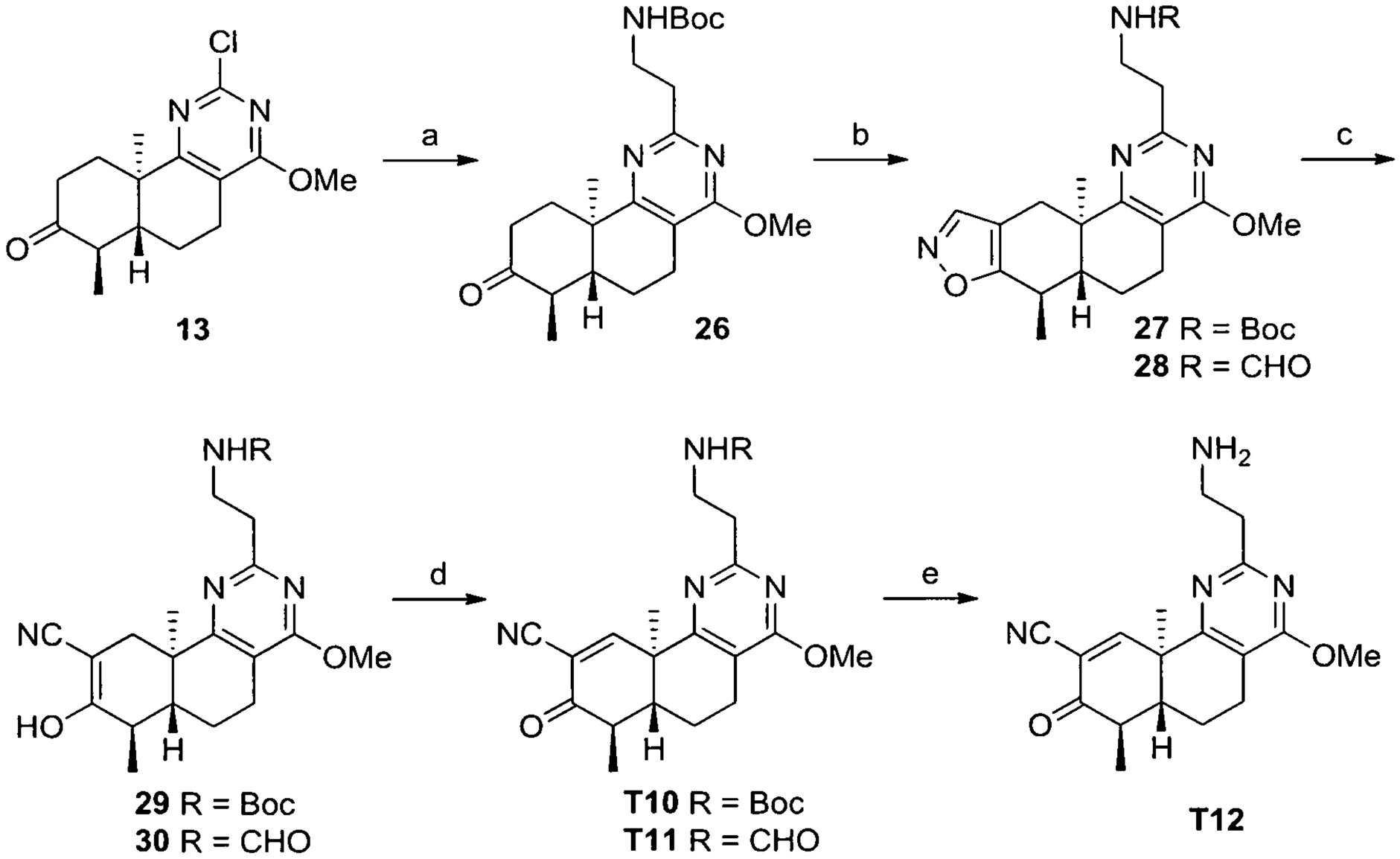
Reagents and conditions: a) 4-pyridinamine, Cs_2CO_3, Xantphos, $Pd_2(dba)_3$, 1,4-dioxane, 100 °C; b) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, H_2O, 55 °C; c) NaOMe, MeOH, 55 °C; d) DDQ, benzene, 85 °C.

Scheme 5



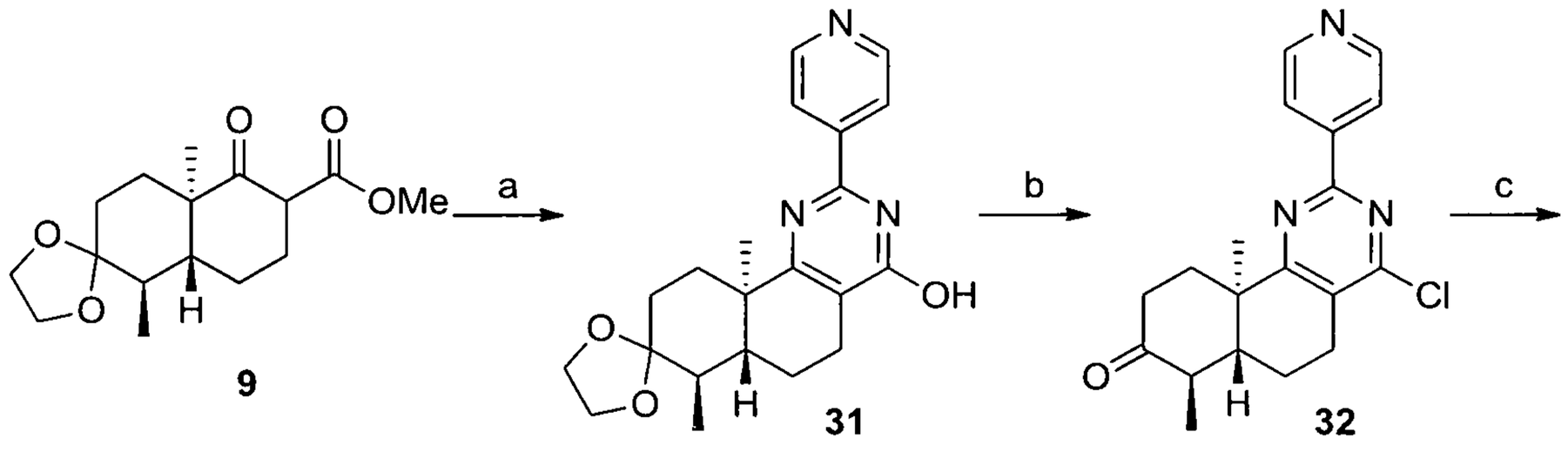
Reagents and conditions: a) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, H_2O, 55 °C; b) quinoline-4-boronic acid, Ph_3P, K_3PO_4, $Pd(OAc)_2$, DME, DMF, microwave, 110 °C; c) NaOMe, MeOH, 55 °C; d) DDQ, benzene, 85 °C.

Scheme 6



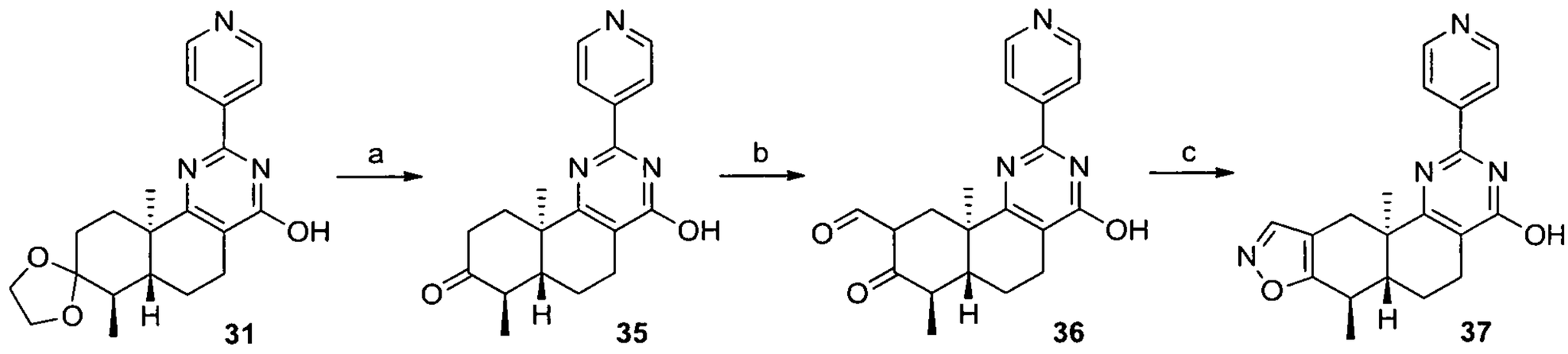
Reagents and conditions: a) $K^+BF_3^-(CH_2)_2NHBoc$, Cs_2CO_3, $Pd(dppf)Cl_2$, toluene, H_2O, 100 °C; b) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, H_2O, 55 °C; c) NaOMe, MeOH, 55 °C; d) DDQ, toluene, 90 °C; e) TFA, THF, rt.

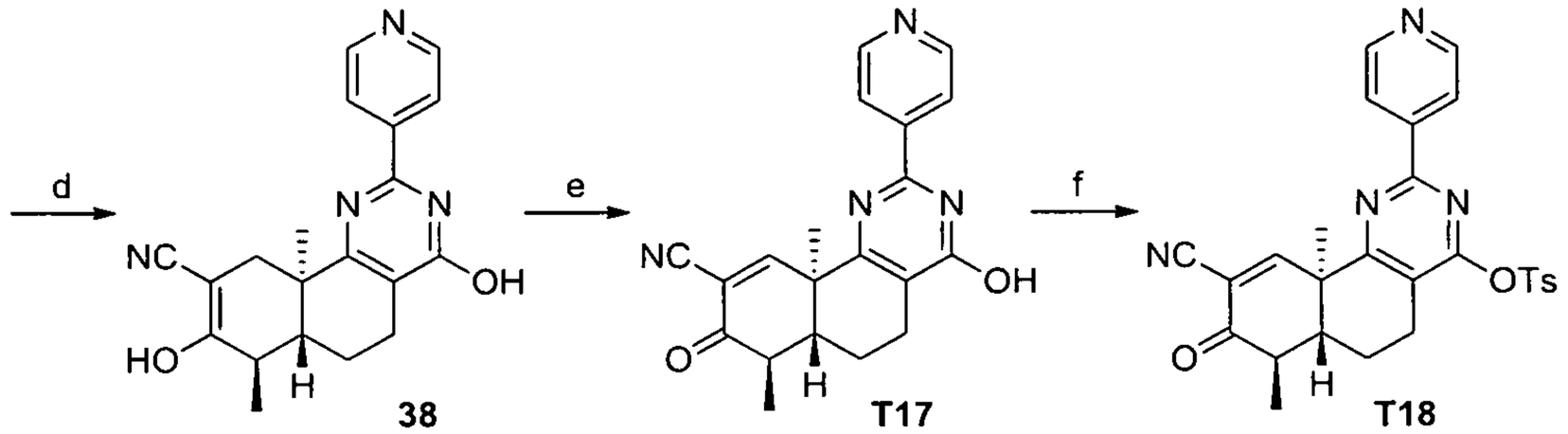
Scheme 7



Reagents and conditions: a) 4-amidinopyridine hydrochloride, K_2CO_3, EtOH, rt; b) $POCl_3$, toluene, 100 °C; c) $PhB(OH)_2$, Na_2CO_3, $Pd(dppf)Cl_2$, 1,4-dioxane, H_2O, microwave, 100 °C; d) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, H_2O, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C; g) hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II), EtOH, H_2O, reflux.

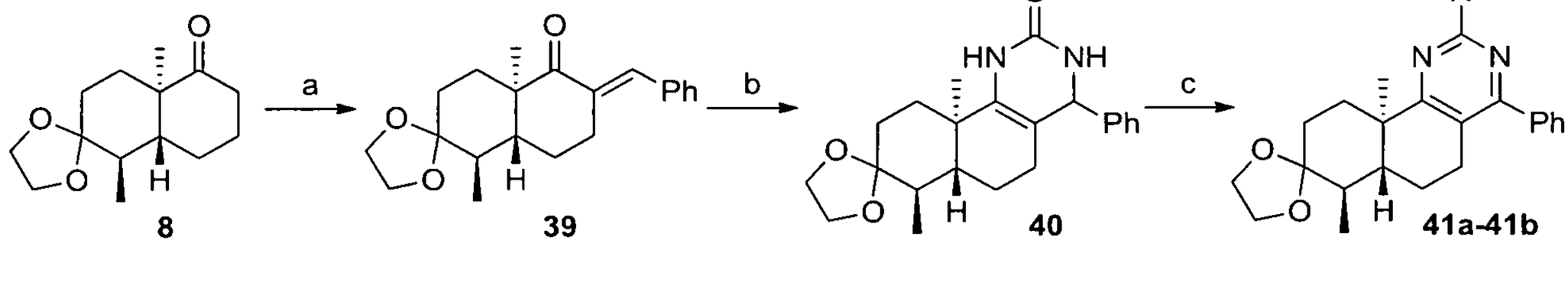
Scheme 8

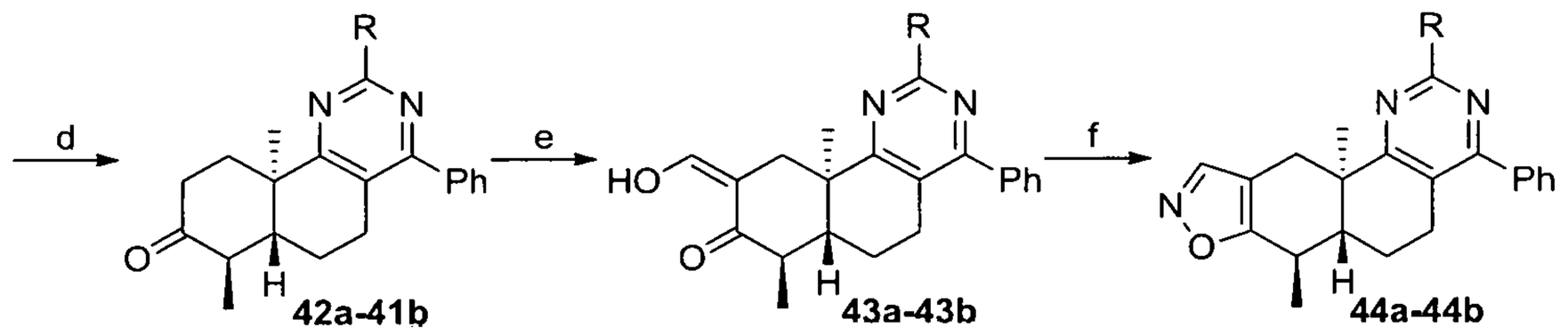


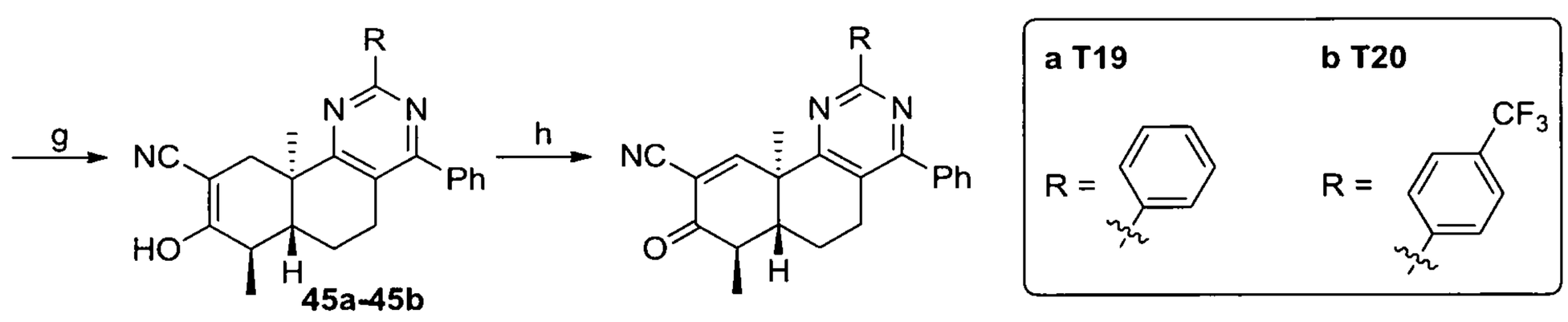


Reagents and conditions: a) aq. 3 N HCl, THF, MeOH, rt; b) HCO_2Et, NaOMe, MeOH, rt; c) $NH_2OH{\cdot}HCl$, AcOH, EtOH, 60 °C-rt; d) NaOMe, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C; f) TsCl, pyridine, DMAP, CH_2Cl_2, rt.

Scheme 9

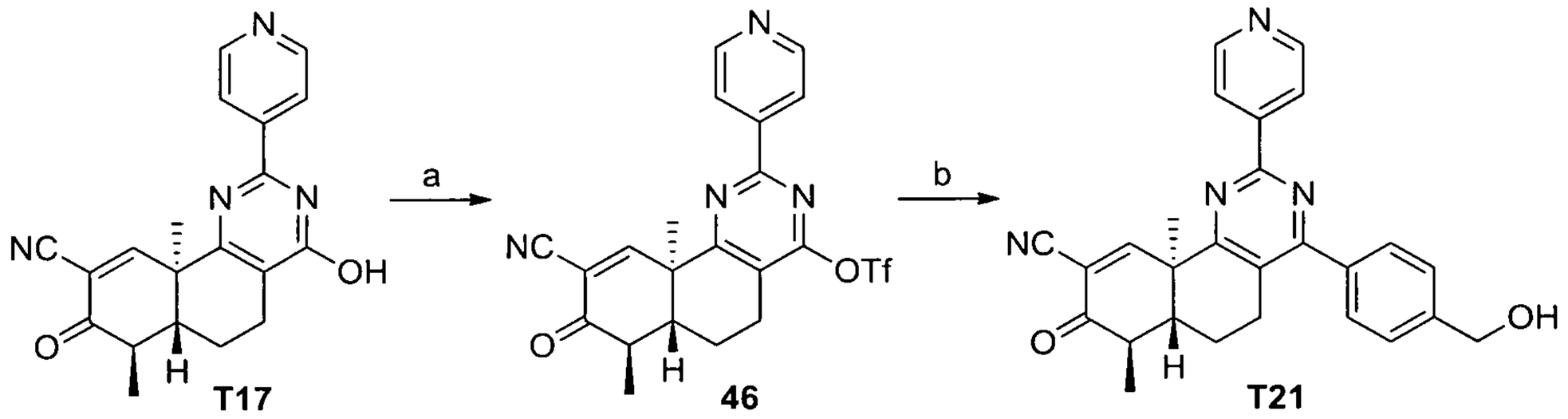






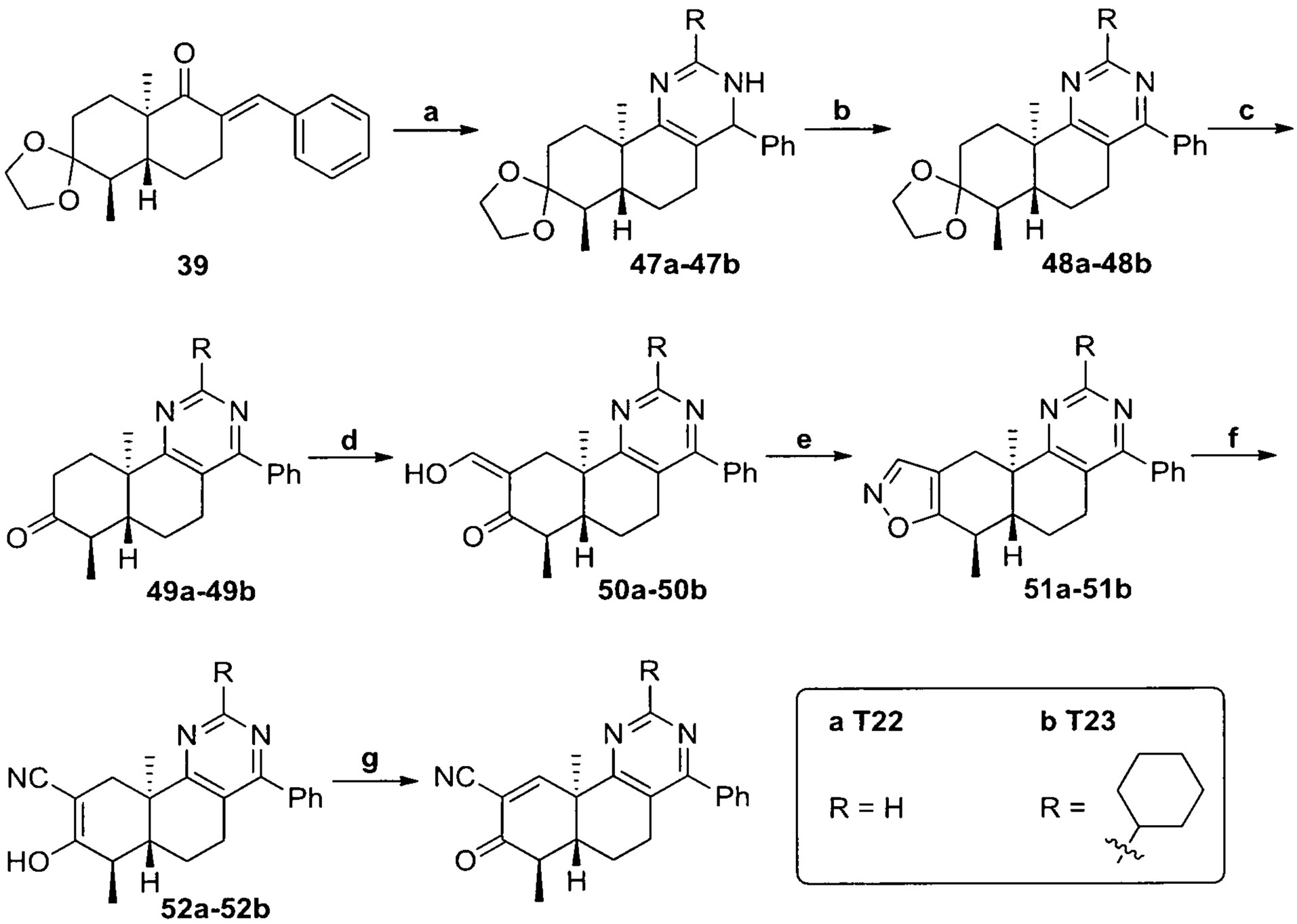
Reagents and conditions: a) PhCHO, NaOMe, THF, rt; b) thiourea, $KOBu^t$, EtOH, reflux; c) $RB(OH)_2$, copper(I) thiophene-2-carboxylate, $Pd(PPh_3)_4$, 1,4-dioxane, 100 °C; d) aq. 3 N HCl, THF, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH{\cdot}HCl$, EtOH, 50 °C; g) NaOMe, MeOH, THF, rt; h) i) Br_2, DMF/CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

Scheme 10



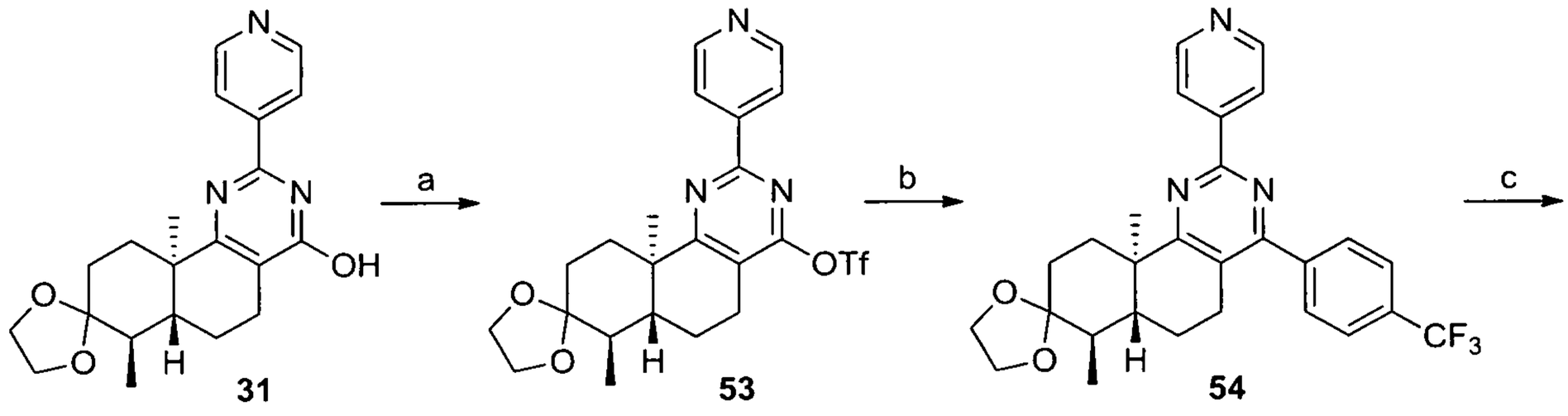
Reagents and conditions: a) Tf_2O, Et_3N, CH_2Cl_2, 0 °C; b) 4-CH_2OH-$PhB(OH)_2$, K_2CO_3, $Pd(dppf)Cl_2$, 1,4-dioxane, 90 °C.

Scheme 11



Reagents and conditions: a) $RC(NH)NH_2$, $KOBu^t$, EtOH, reflux; b) MnO_2, CH_2Cl_2, rt; c) aq. 3 N HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 50 °C; f) NaOMe, MeOH, THF, rt; g) i) Br_2, DMF, CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

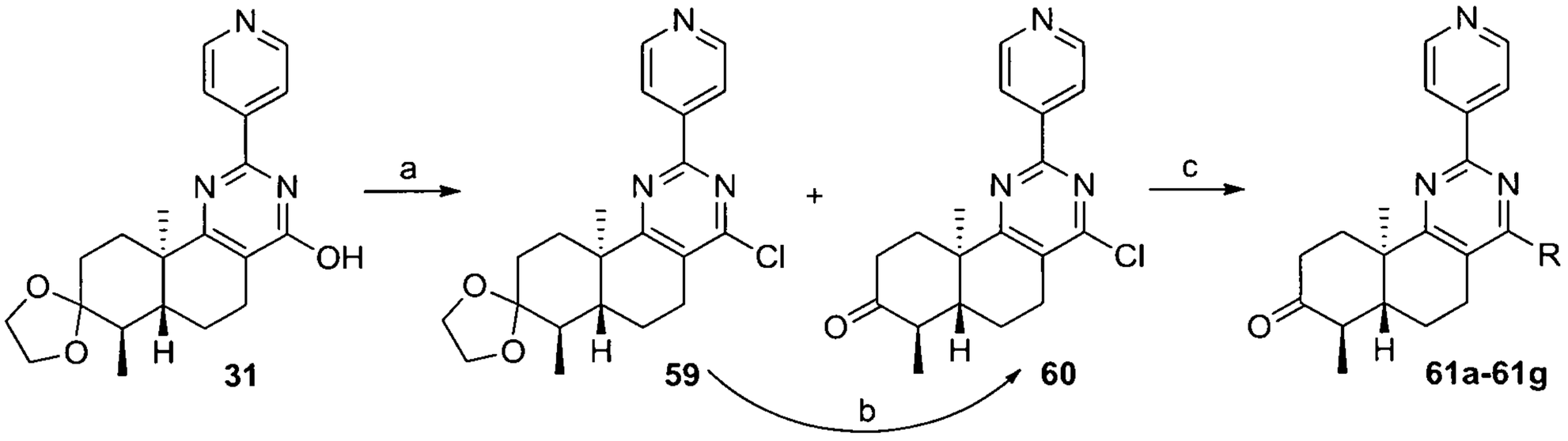
Scheme 12



31 53 54 55 56 57 58 T24

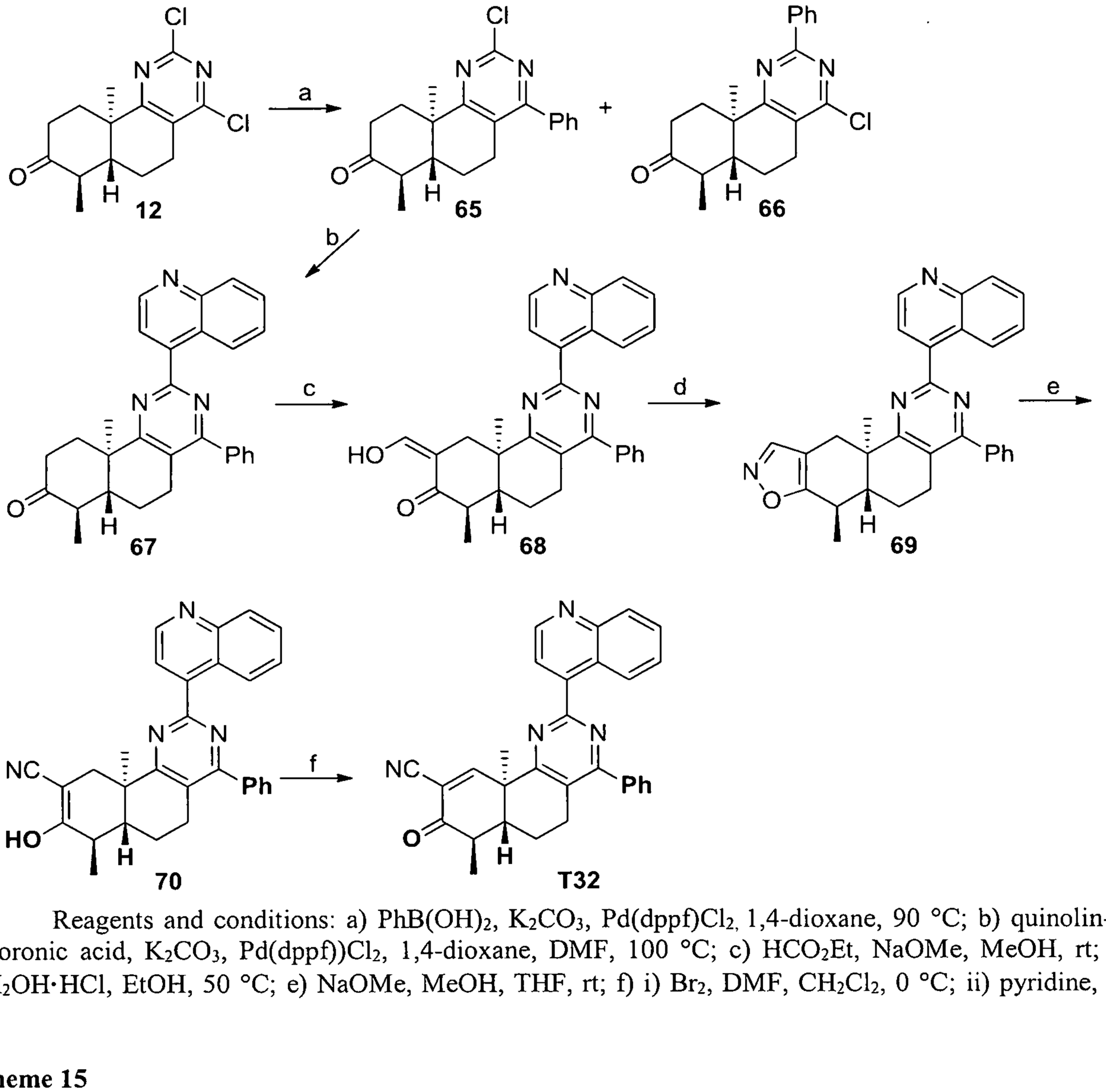
Reagents and conditions: a) Tf_2O, Et_3N, CH_2Cl_2, 0 °C; b) 4-CF_3-$PhB(OH)_2$, K_3PO_4, $Pd(PPh_3)_4$, DME, 90 °C; c) aq. 3 N HCl, MeOH, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 60 °C-rt; f) NaOMe, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 13



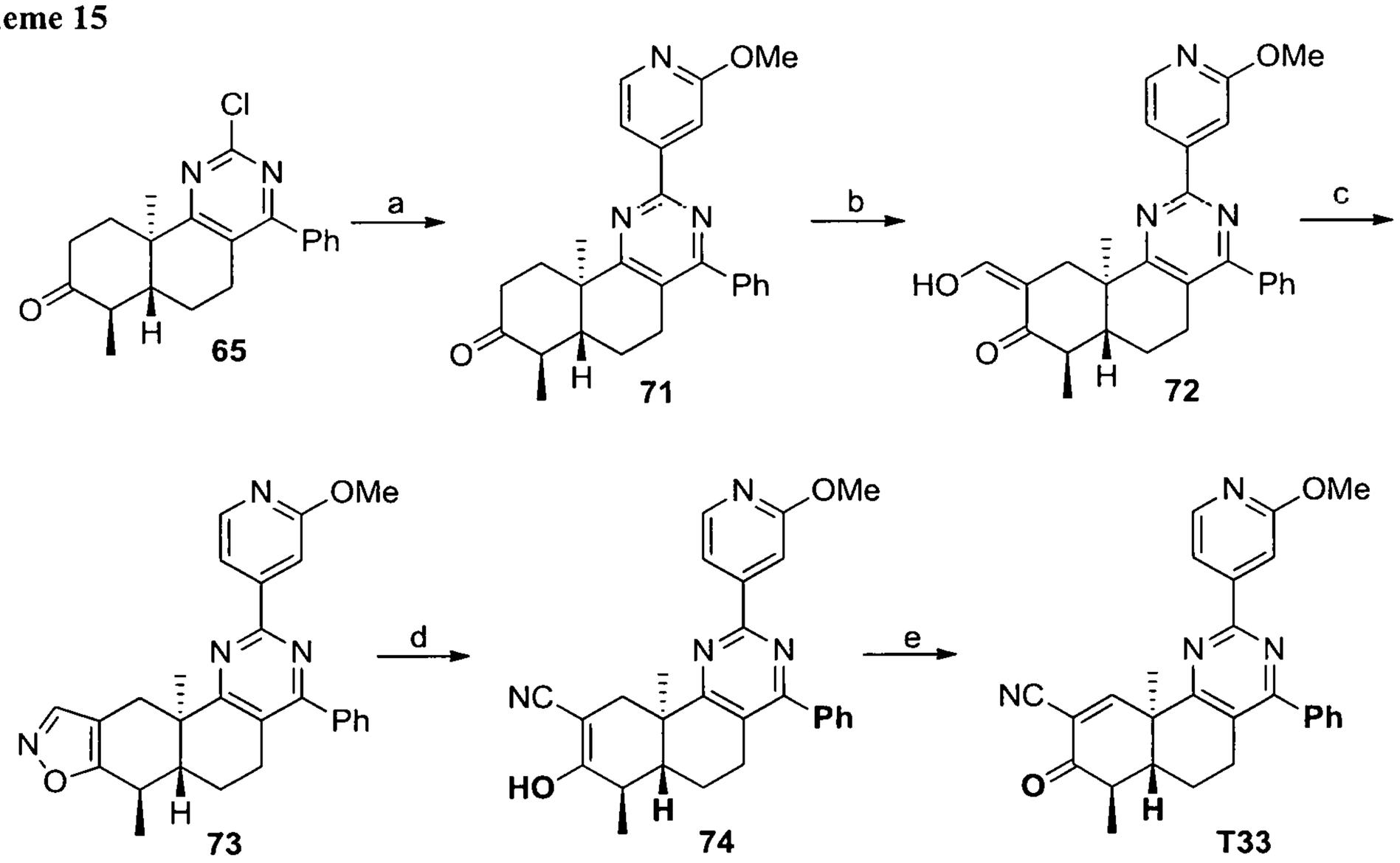
Reagents and conditions: a) $POCl_3$, toluene, 100 °C; b) aq. 3 N HCl, MeOH, THF, rt; c) $RB(OH)_2$, K_3PO_4, $Pd(PPh_3)_4$, solvent, 90 °C; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 60 °C-rt; f) NaOMe, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 14



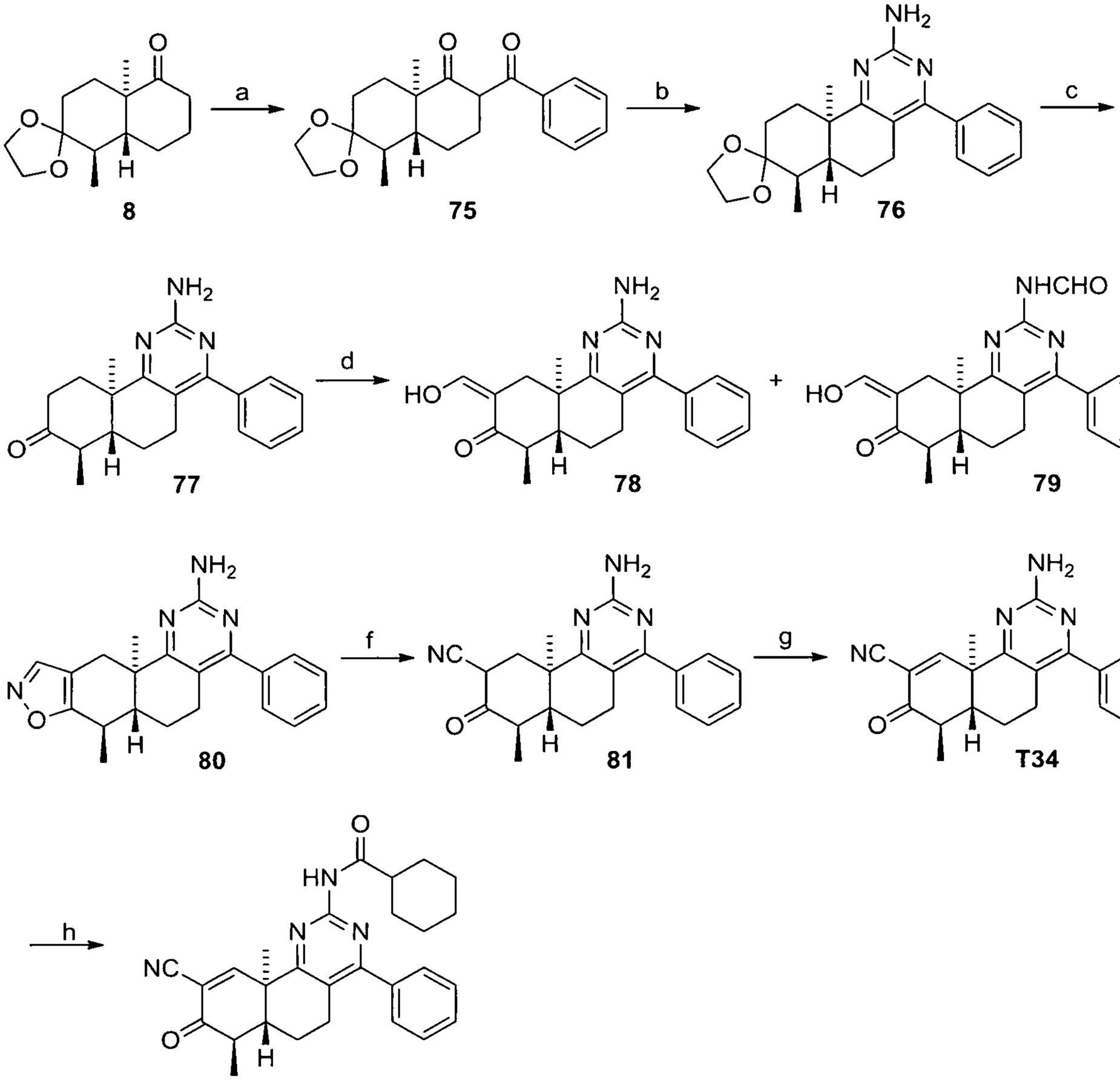
Reagents and conditions: a) $PhB(OH)_2$, K_2CO_3, $Pd(dppf)Cl_2$, 1,4-dioxane, 90 °C; b) quinolin-4-ylboronic acid, K_2CO_3, $Pd(dppf))Cl_2$, 1,4-dioxane, DMF, 100 °C; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH{\cdot}HCl$, EtOH, 50 °C; e) NaOMe, MeOH, THF, rt; f) i) Br_2, DMF, CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

Scheme 15



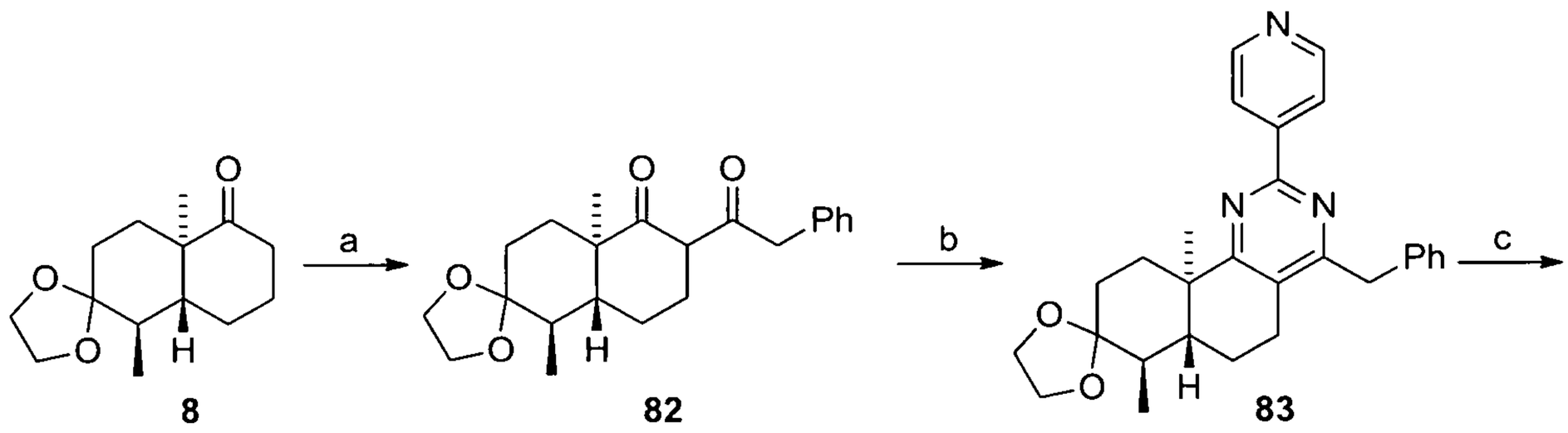
Reagents and conditions: a) 2-methoxypyridine-4-boronic acid, K_2CO_3, Pd(dppf))Cl_2, 1,4-dioxane, DMF, 100 °C; b) HCO_2Et, NaOMe, MeOH, rt; c) $NH_2OH \cdot HCl$, EtOH, 50 °C; d) NaOMe, MeOH, THF, rt; e) i) Br_2, DMF, CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

Scheme 16



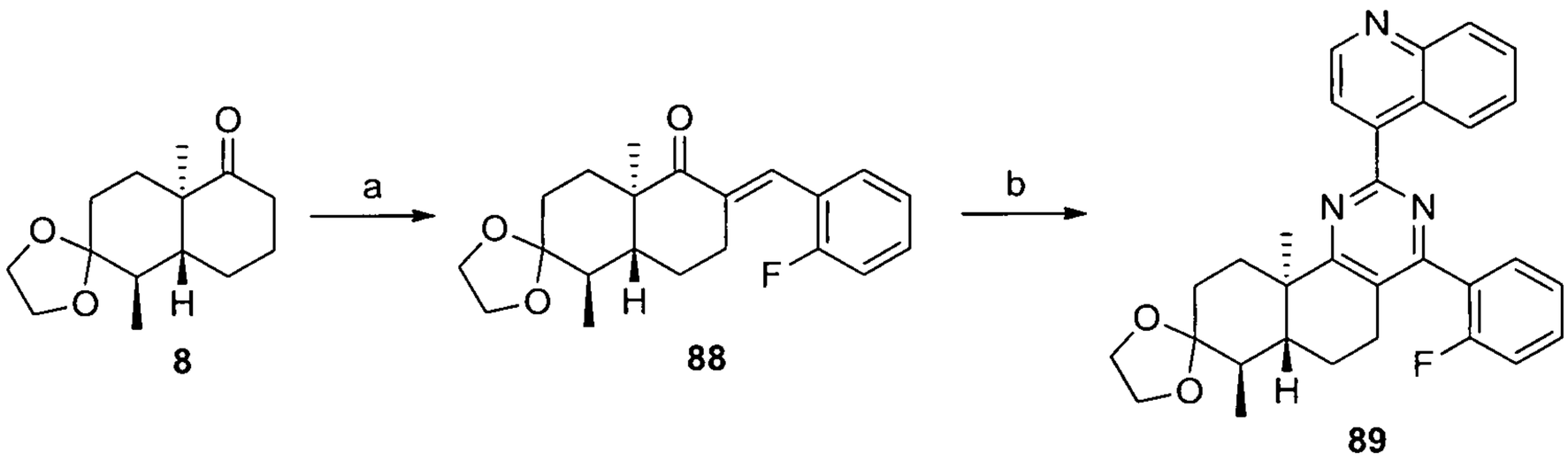
Reagents and conditions: a) $MgBr_2 \cdot OEt_2$, DIPEA, PhCOCl, CH_2Cl_2, rt; b) guanidine carbonate, NaOMe, EtOH, reflux; c) aq. 1 N HCl, MeOH, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, H_2O, rt; f) NaOMe, MeOH, THF, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 65 °C; h) cyclohexanecarbonyl chloride, pyridine, CH_2Cl_2, rt.

Scheme 17



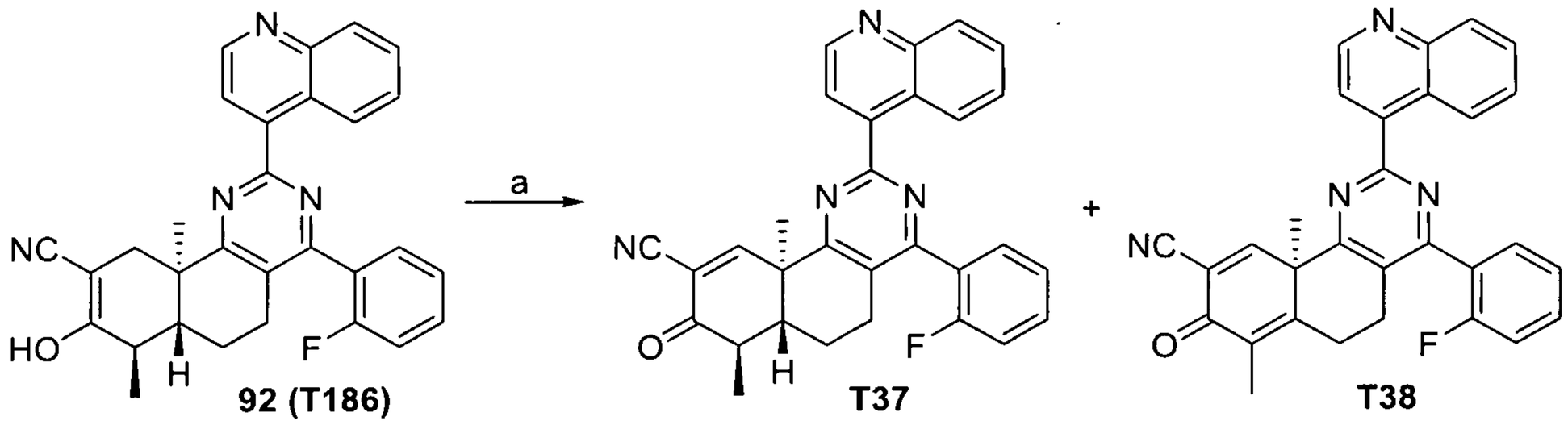
Reagents and conditions: a) $MgBr_2 \cdot OEt_2$, DIPEA, $PhCH_2COCl$, CH_2Cl_2, rt; b) amidinopyridine hydrochloride, K_2CO_3, EtOH, rt; c) aq. 3 N HCl, MeOH, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 60 °C-rt; f) NaOMe, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 18



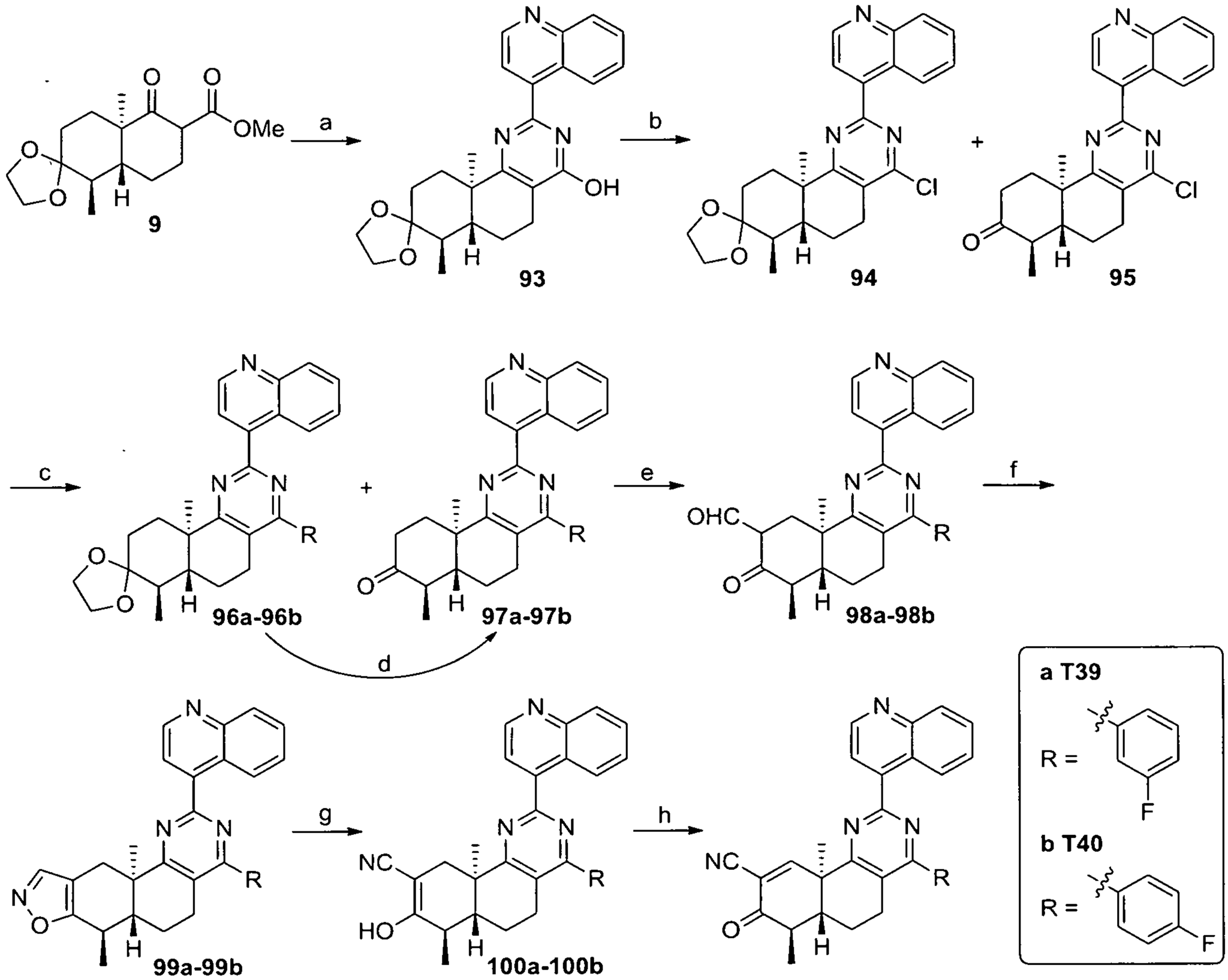
Reagents and conditions: a) 2-fluorobenzaldehyde, KF/Al_2O_3, EtOH, rt; b) i) 4-quinolinecarboximidamide hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; or ii) DDQ, CH_2Cl_2, rt; c) aq. 3 N HCl, THF, rt; d) i) HCO_2Et, NaOMe, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 19



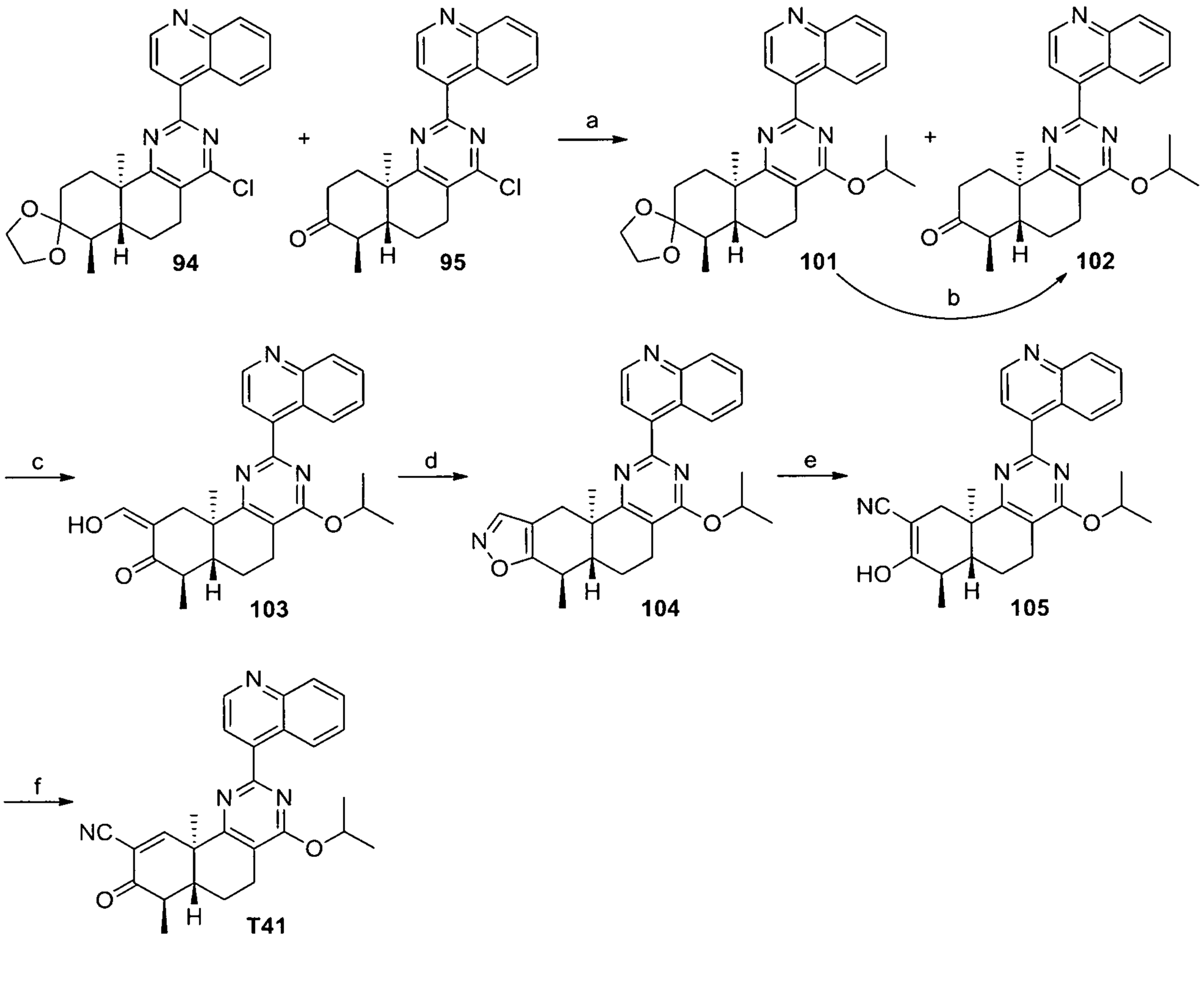
Reagents and conditions: a) i) Br_2, DMF, CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

Scheme 20



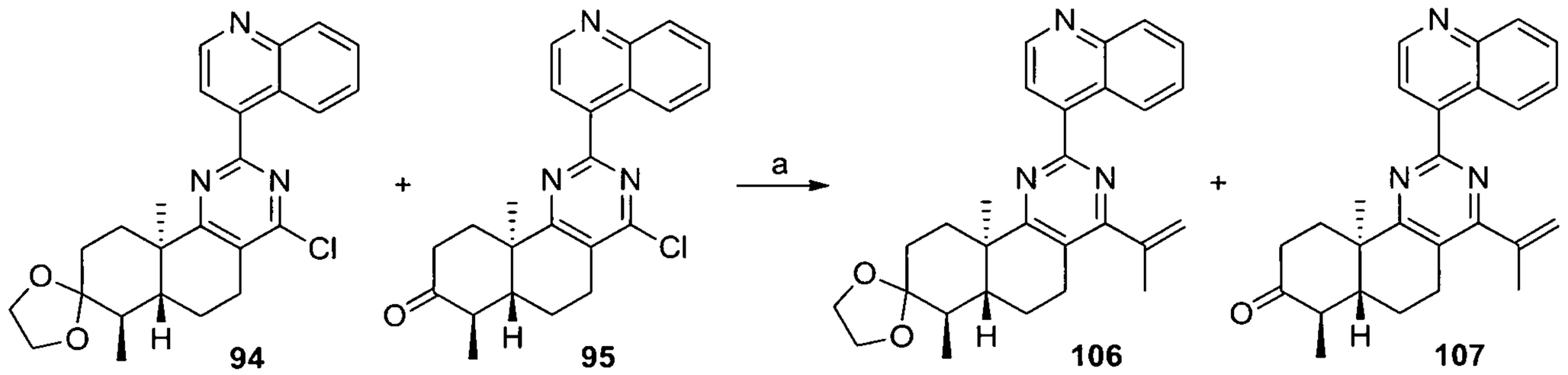
Reagents and conditions: a) quinoline-4-carboximidamide hydrochloride, K_2CO_3, EtOH, rt; b) $POCl_3$, toluene, microwave, 100 °C; c) $RB(OH)_2$, $Pd(dppf)Cl_2$, K_2CO_3, 1,4-dioxane, 90 °C; d) aq. 3 N HCl, THF, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, EtOH, 50 °C; g) NaOMe, MeOH, THF, rt; h) i) Br_2, DMF, CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

Scheme 21



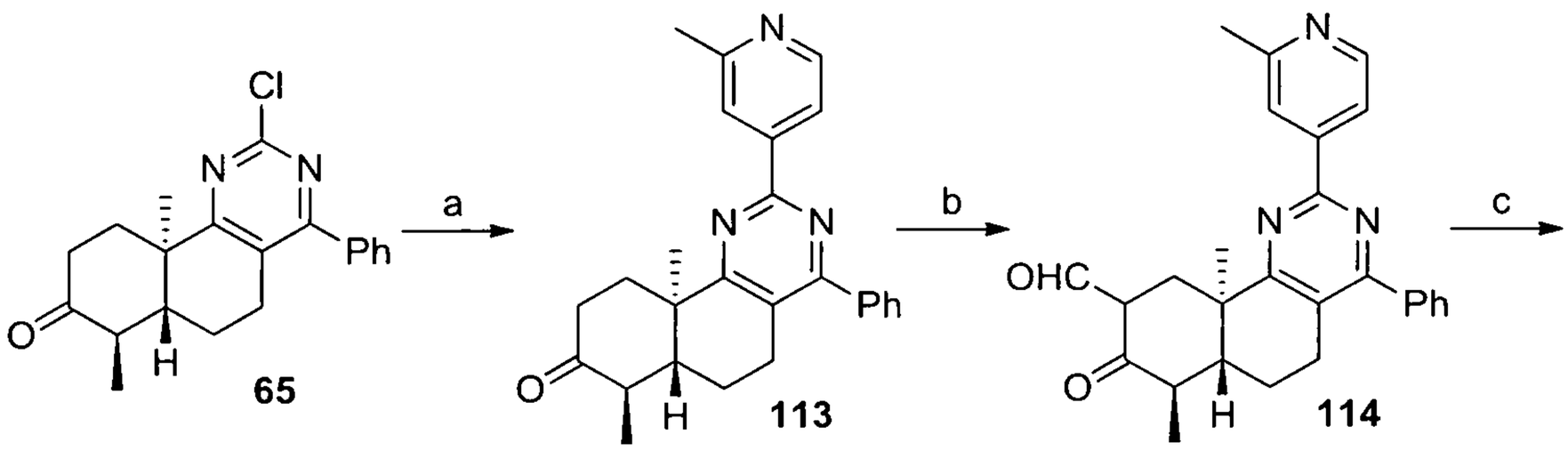
Reagents and conditions: a) 2-propanol, NaH, THF, rt; b) aq. 3 N HCl, THF, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH \cdot HCl$, EtOH, 50 °C; e) NaOMe, MeOH, THF, rt; f) i) Br_2, DMF, CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

Scheme 22



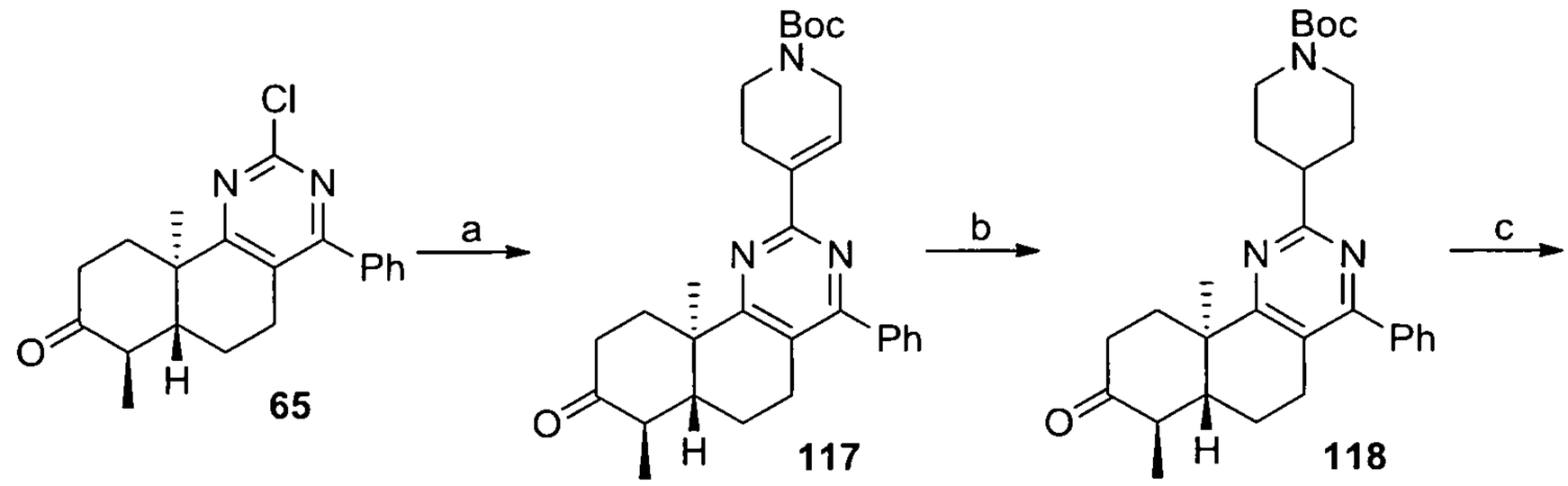
Reagents and conditions: a) 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane, $Pd(dppf)Cl_2$, K_2CO_3, 1,4-dioxane, 90 °C; b) H_2, 10% Pd/C, THF, rt; c) aq. 3 N HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 50 °C; f) NaOMe, MeOH, THF, rt; g) i) Br_2, DMF, CH_2Cl_2, 0 °C; ii) pyridine, 50 °C.

Scheme 23



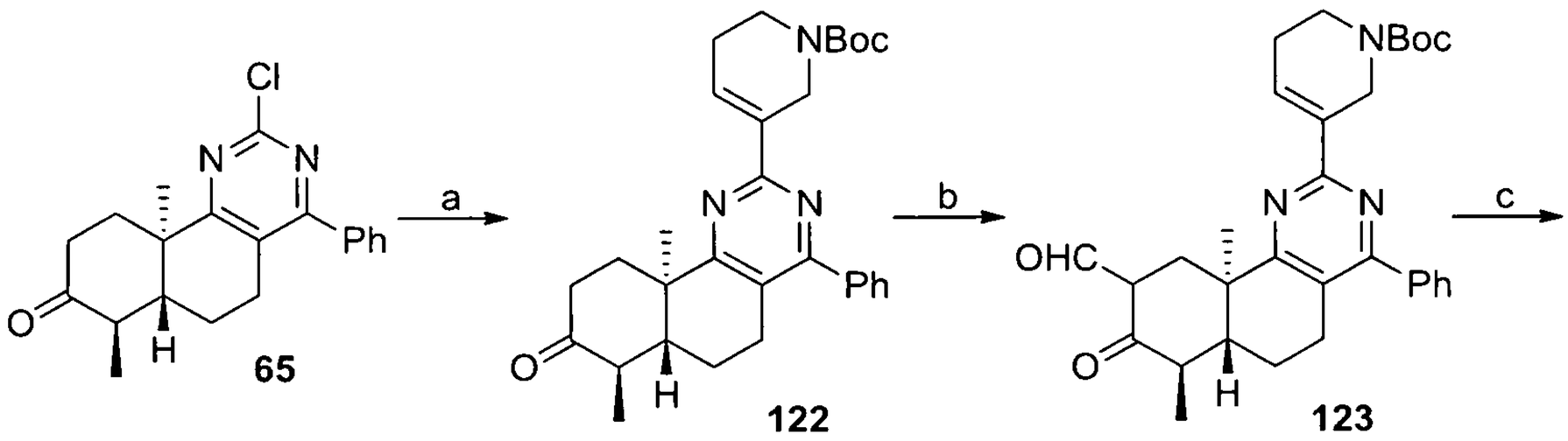
Reagents and conditions: a) 2-methylpyridine-4-boronic acid, $Pd(dppf)Cl_2$, K_2CO_3, 1,4-dioxane, DMF, 90 °C; b) HCO_2Et, NaOMe, MeOH, rt; c) $NH_2OH \cdot HCl$, EtOH, 60 °C-rt; d) NaOMe, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

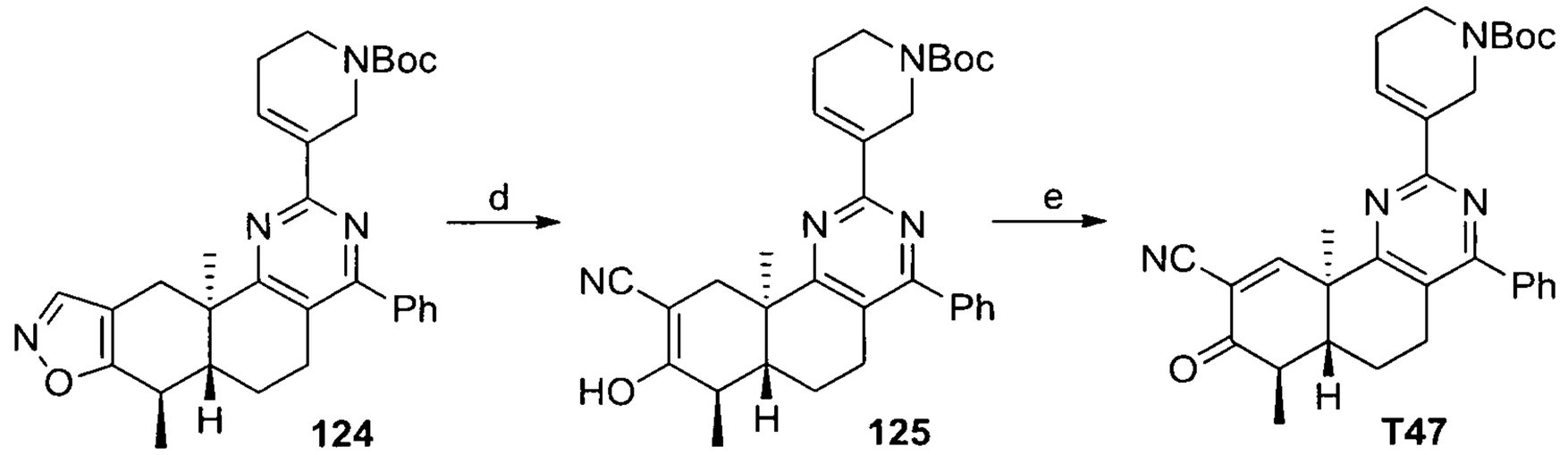
Scheme 24

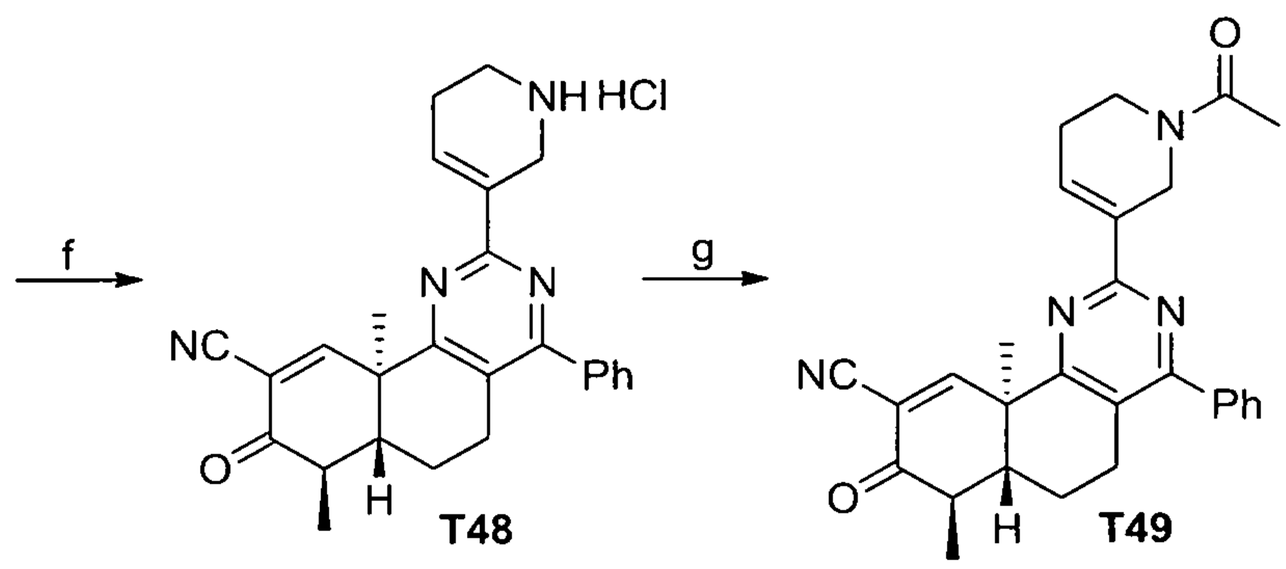


Reagents and conditions: a) *N*-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, 90 °C; b) 10% Pd/C, H_2, EtOAc, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH \cdot HCl$, EtOH, 60 °C-rt; e) NaOMe, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C; g) HCl, 1,4-dioxane, CH_2Cl_2, rt; h) NaOAc, Ac_2O, rt.

Scheme 25

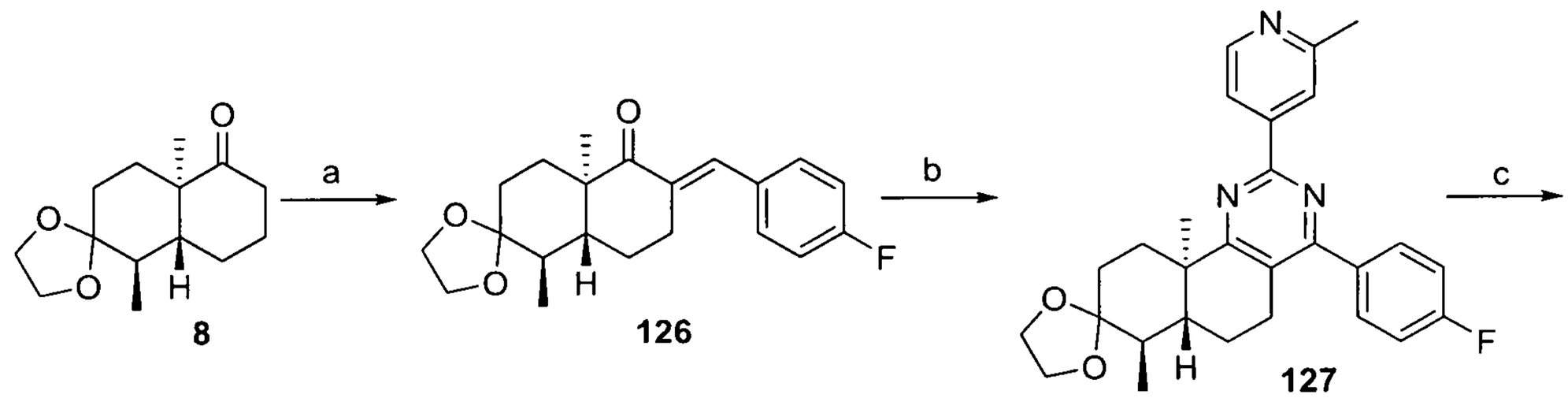


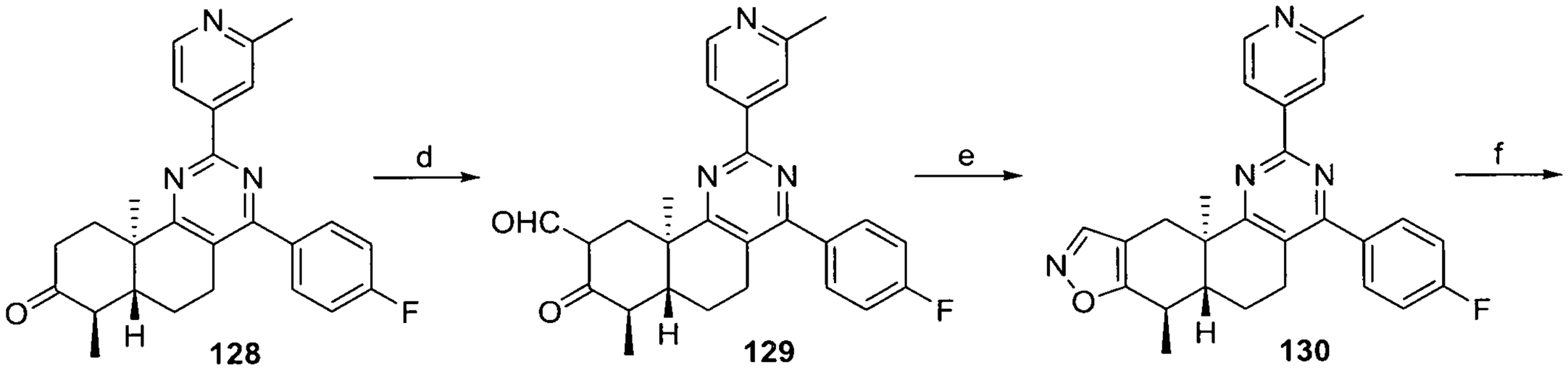


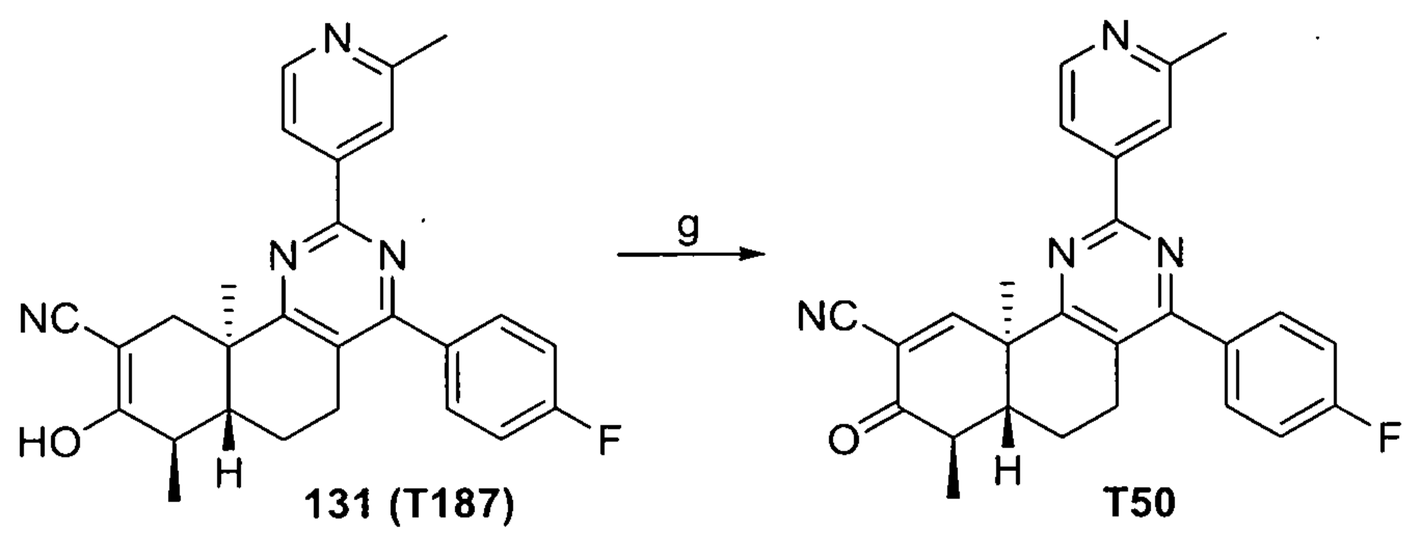


Reagents and conditions: a) *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(*2H*)-carboxylate, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, 90 °C; b) HCO_2Et, NaOMe, MeOH, rt; c) $NH_2OH \cdot HCl$, EtOH, 60 °C-rt; d) NaOMe, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C; f) HCl, 1,4-dioxane, CH_2Cl_2, rt; g) NaOAc, Ac_2O, rt.

Scheme 26

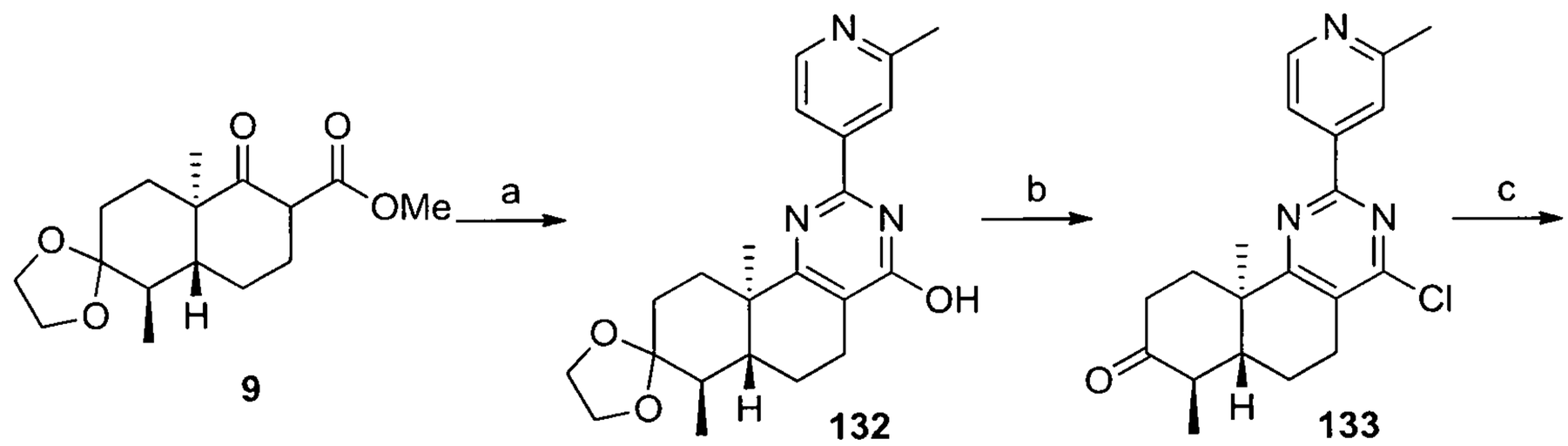






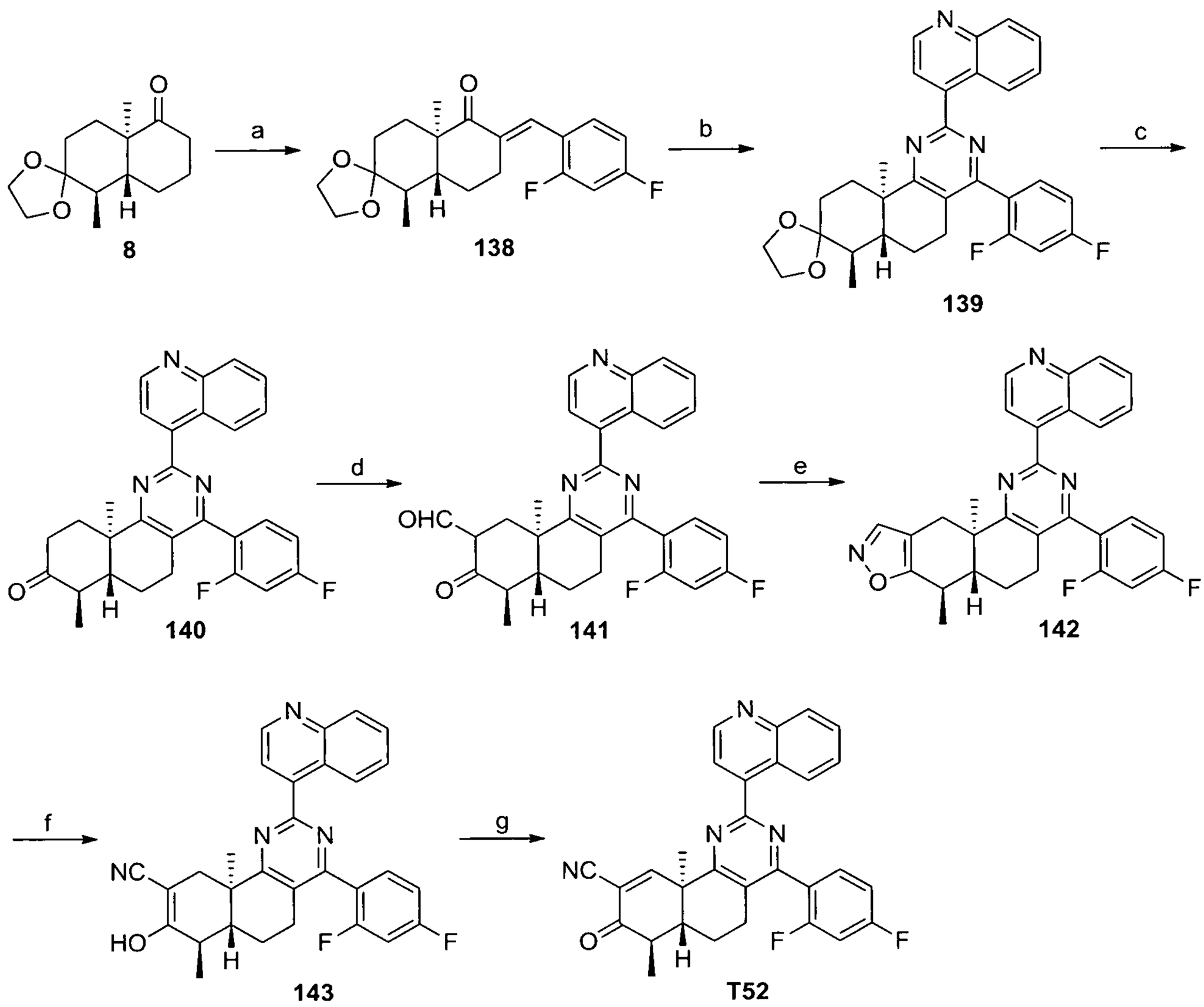
Reagents and conditions: a) 4-fluorobenzaldehyde, KF/Al_2O_3, 2-PrOH, 60 °C-rt; b) i) 2-methyl-4-pyridinecarboximidamide hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; c) aq. 3 N HCl, MeOH, rt; d) HCO_2Et, NaOMe, 0 °C to rt; e) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C-rt; f) K_2CO_3, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 27



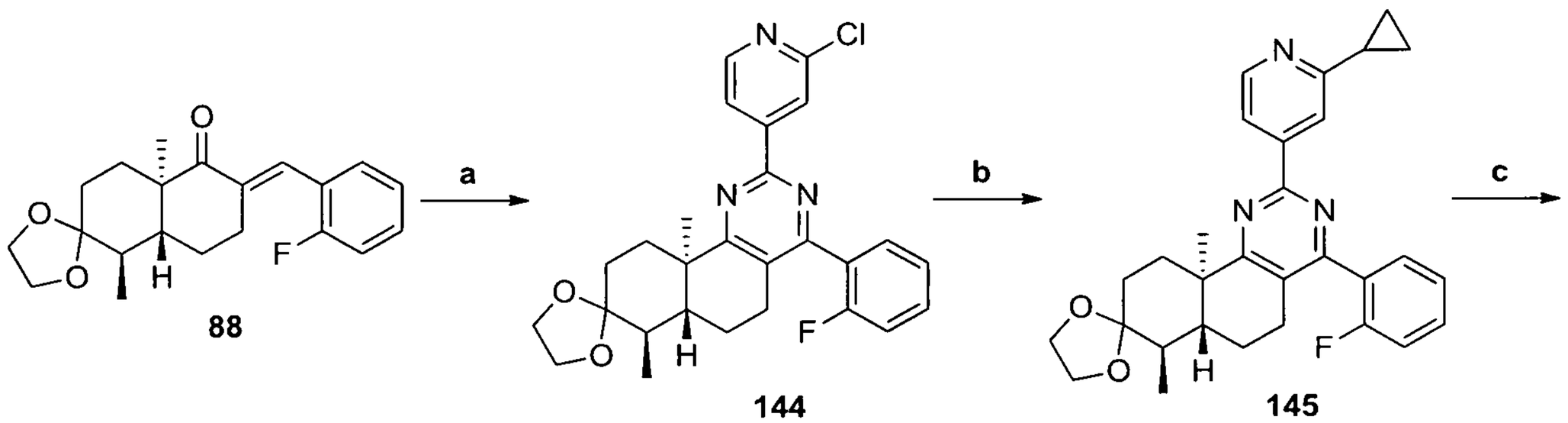
Reagents and conditions: a) 2-methyl-4-pyridinecarboximidamide hydrochloride, K_2CO_3, EtOH, rt; b) i) $POCl_3$, toluene, microwave, 100 °C; ii) aq. 3 N HCl, MeOH, rt; c) 2-F-PhB(OH)$_2$, K_2CO_3, $Pd(PPh_3)_4$, 1,4-dioxane, microwave, 100 °C; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C-rt; f) NaOMe, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 28



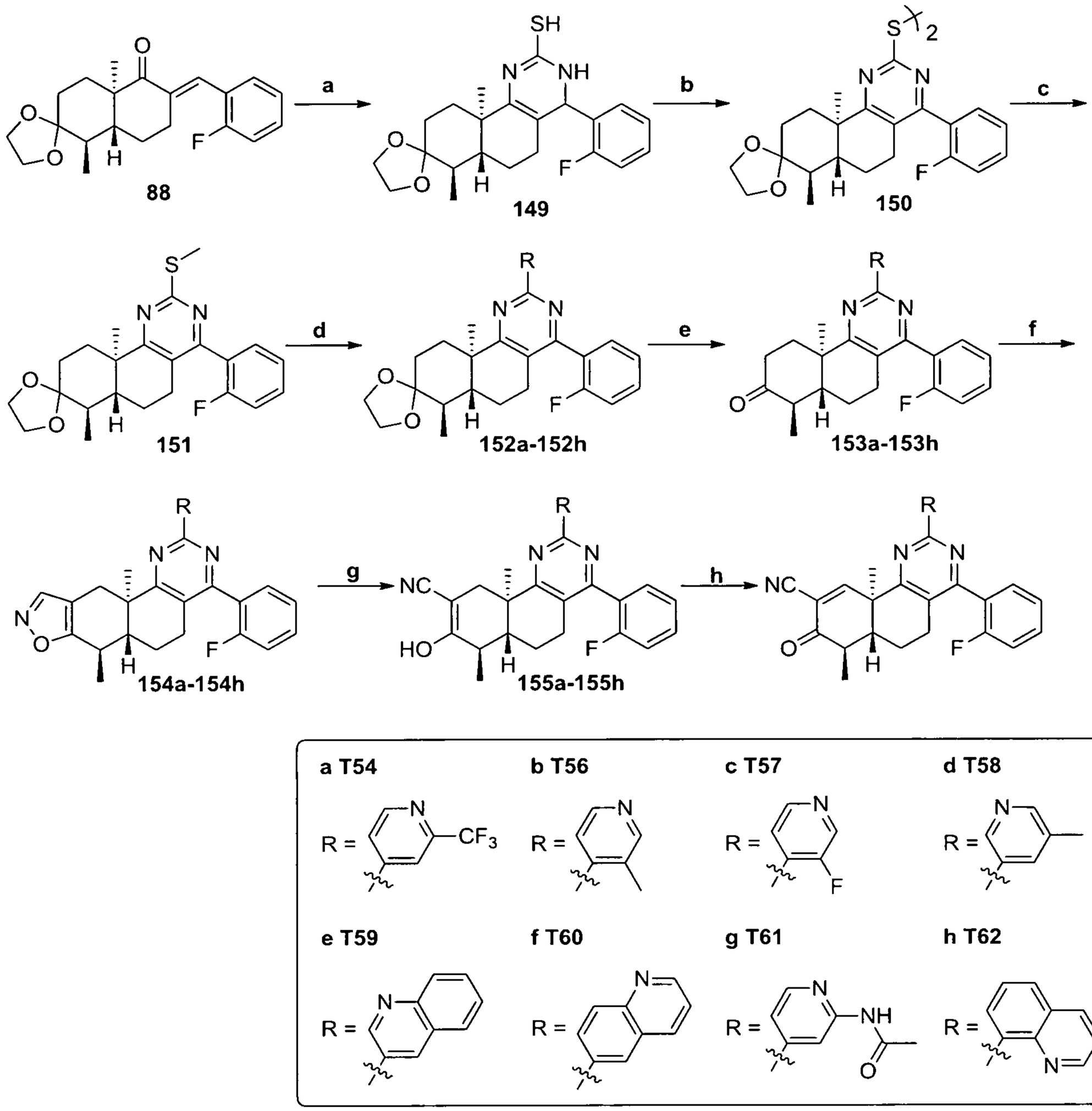
Reagents and conditions: a) 2,4-difluorobenzaldehyde, KF/Al_2O_3, 2-PrOH, 60 °C-rt; b) i) 4-quinolinecarboximidamide hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; c) aq. 3 N HCl, MeOH, rt; d) HCO_2Et, NaOMe, 0 °C to rt; e) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C-rt; f) K_2CO_3, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 29



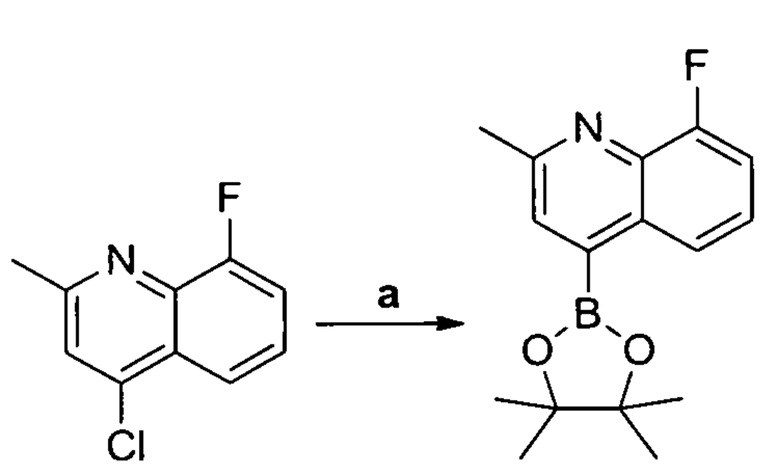
Reagents and conditions: a) i) 2-chloropyridine-4-carboximidamide hydrochloride, K_2CO_3, EtOH, microwave, 120 °C; ii) DDQ, CH_2Cl_2, rt; b) cyclopropylboronic acid, K_3PO_4, $Pd(OAc)_2$, tricyclohexylphosphine, toluene, H_2O, microwave, 130 °C; c) aq. 3 N HCl, THF, MeOH, rt; d) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 30



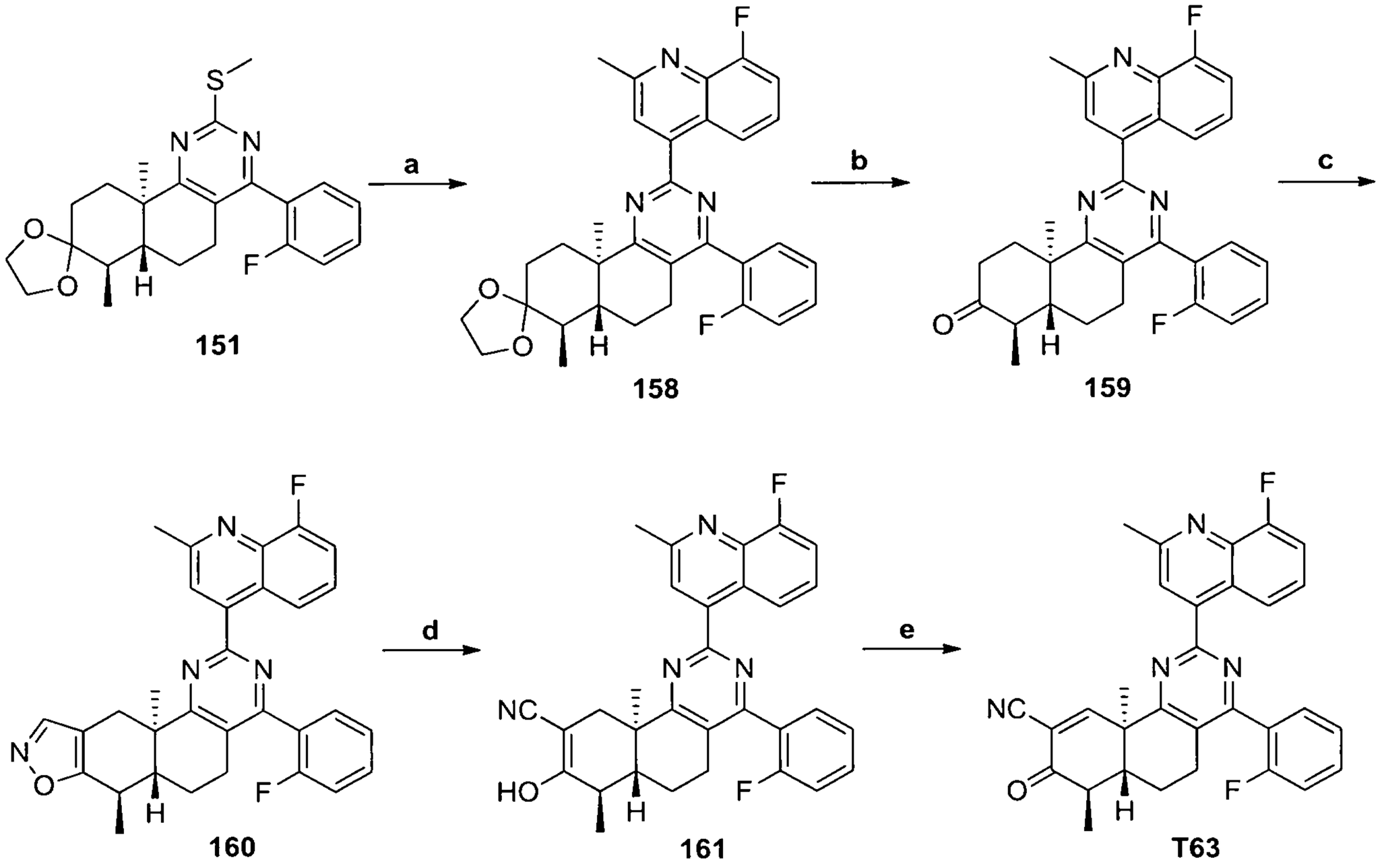
Reagents and conditions: a) thiourea, *t*-BuOK, EtOH, microwave, 120 °C; b) DDQ, CH_2Cl_2, rt; c) $NaBH_4$, MeI, EtOH, THF, 0 °C-rt; d) boronic acid or boronic ester, copper(I) thiophene-2-carboxylate, $Pd(PPh_3)_4$, THF, 100 °C; e) aq. 3 N HCl, THF, MeOH, rt; f) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; g) NaOMe, MeOH, rt or 55 °C; h) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 31



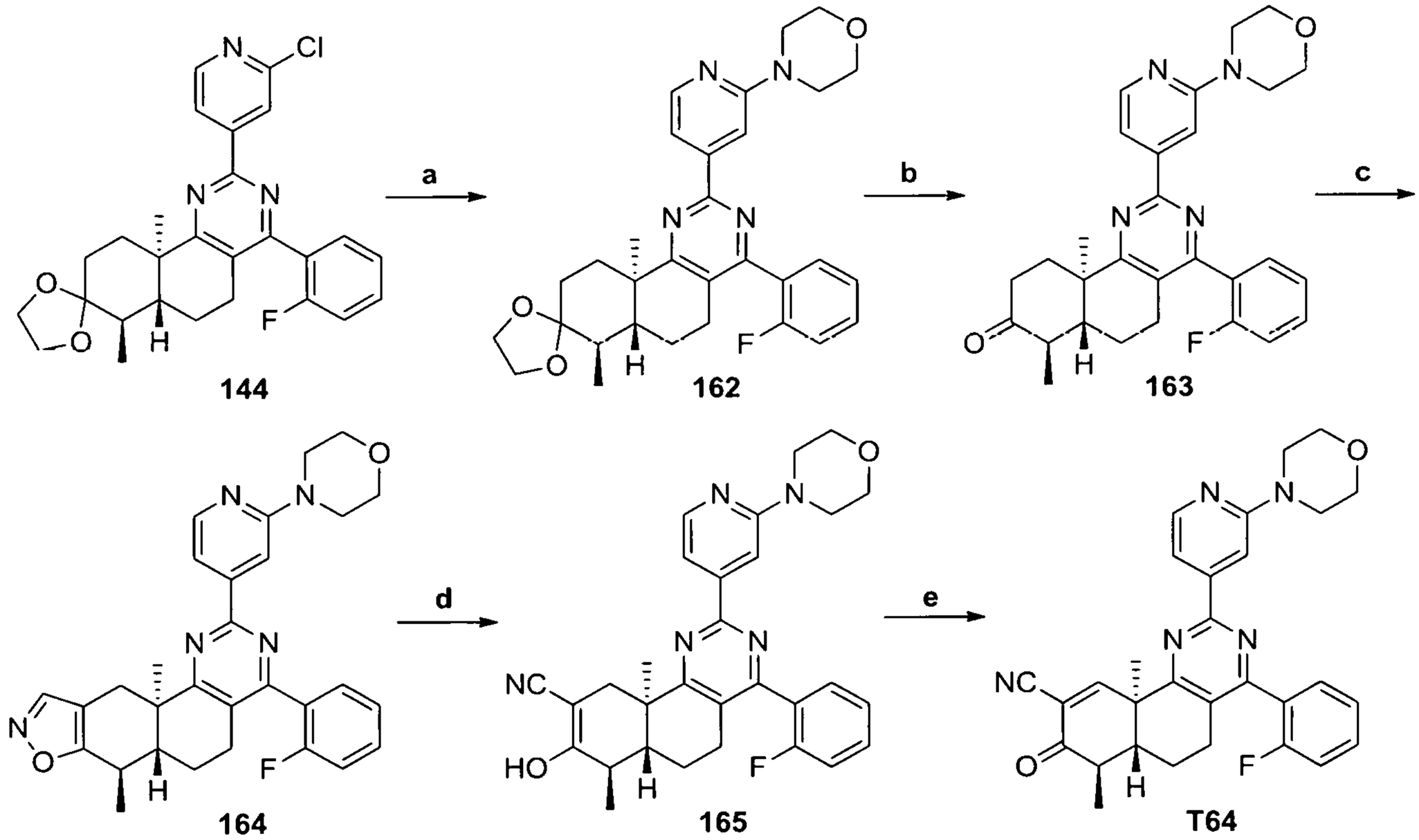
Reagents and conditions: a) bis(pinacolato)diboron, KOAc, $Pd(dppf)Cl_2$, 1,4-dioxane, 125 °C.

Scheme 32



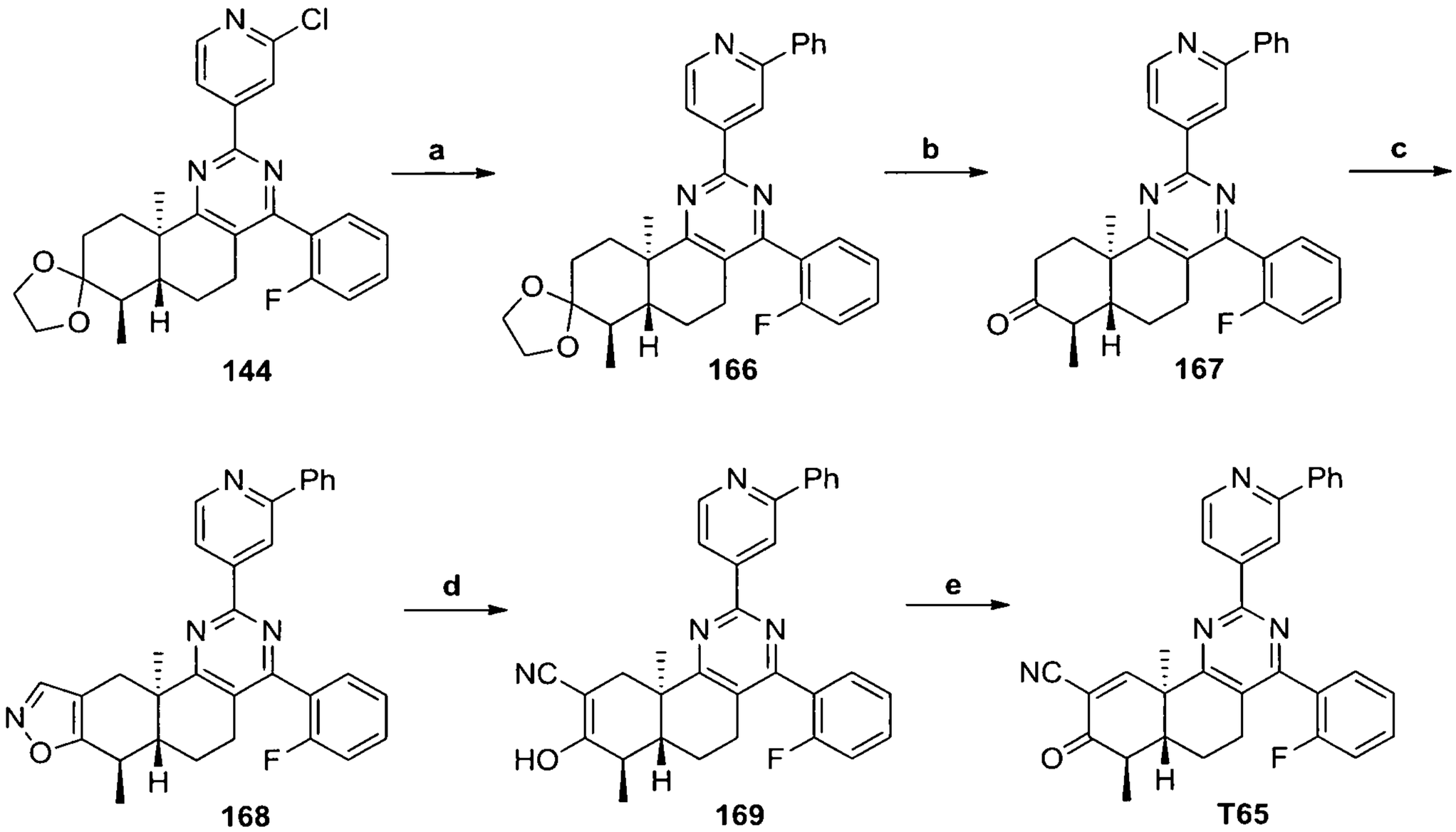
Reagents and conditions: a) **157**, copper(I) thiophene-2-carboxylate, $Pd(PPh_3)_4$, THF, 100 °C; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) K_2CO_3, MeOH, rt; e) DDQ, benzene, 85 °C.

Scheme 33



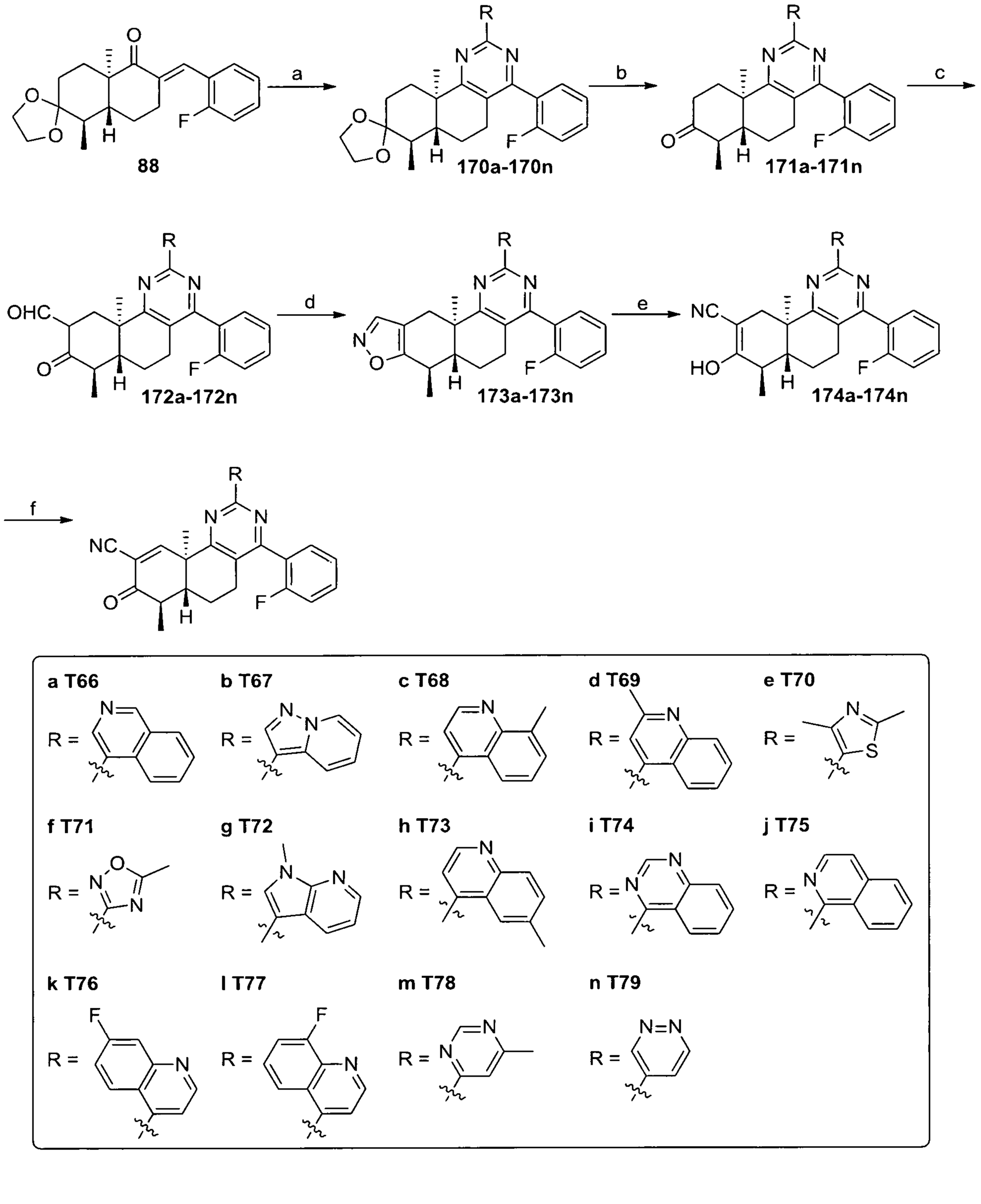
Reagents and conditions: a) morpholine, *t*-BuONa, Xphos, $Pd_2(dba)_3$, toluene, microwave, 100 °C; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) DDQ, benzene, reflux.

Scheme 34



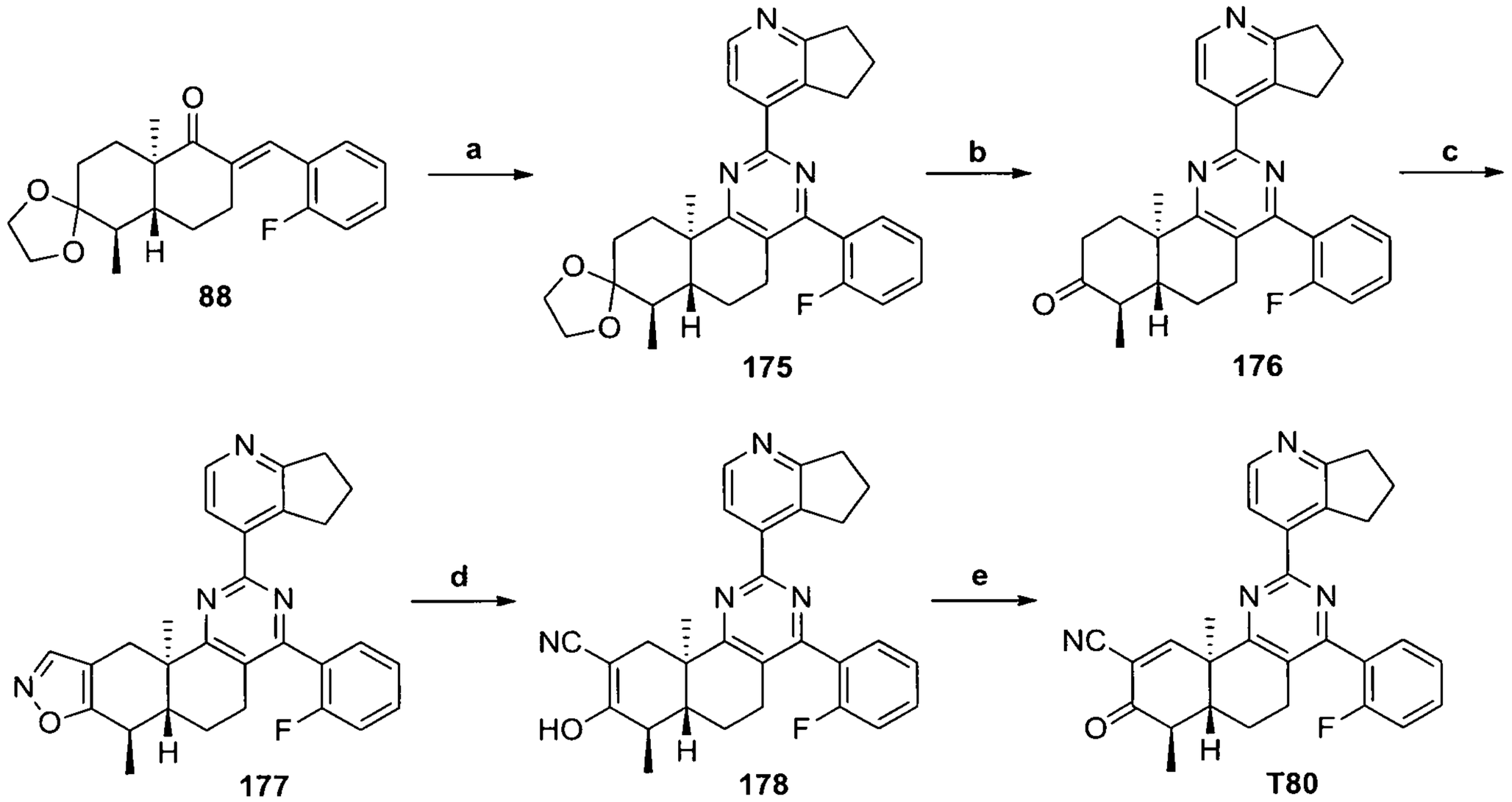
Reagents and conditions: a) $PhB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, toluene, EtOH, H_2O, microwave, 100 °C; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 35



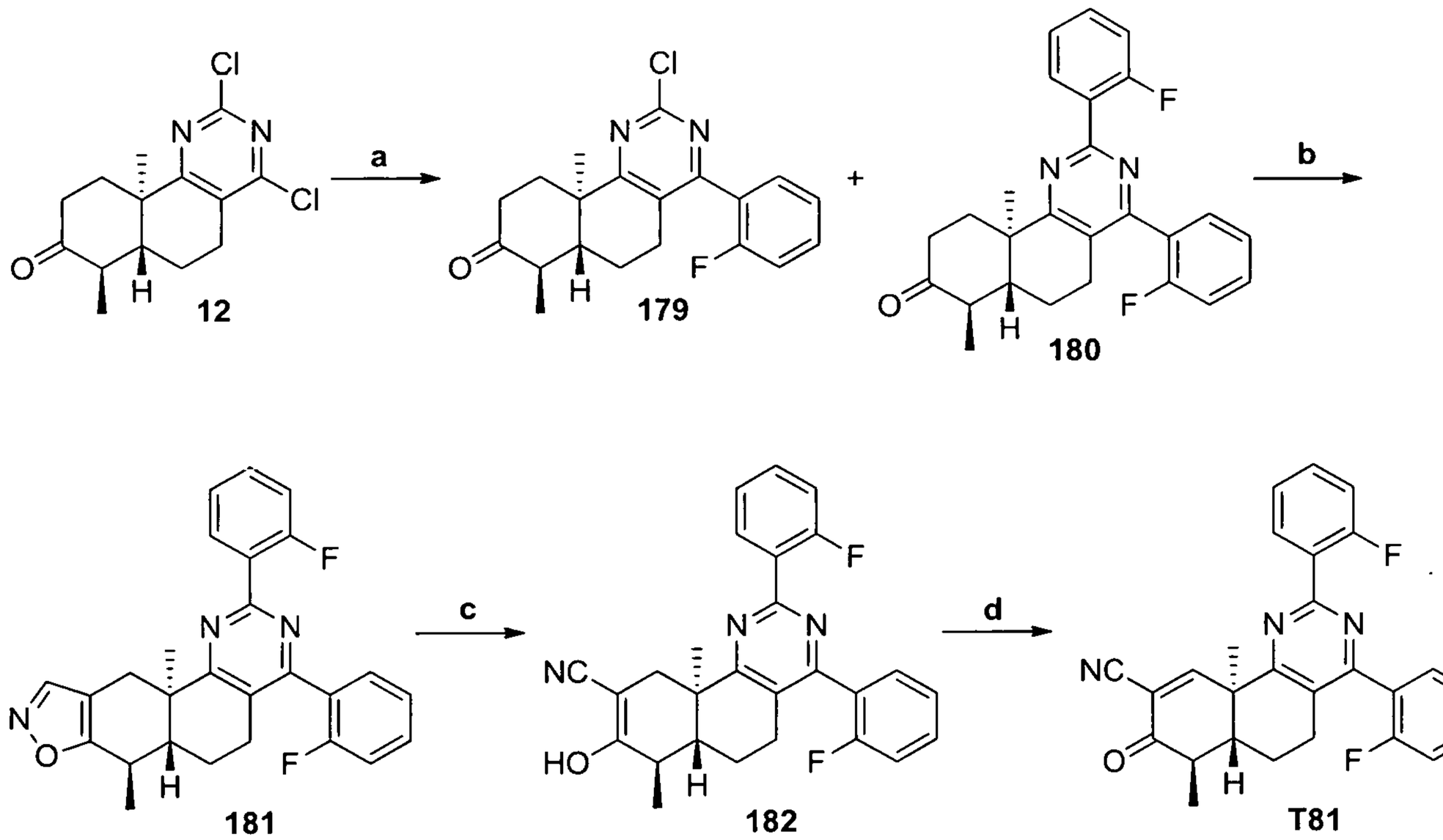
Reagents and conditions: a) i) amidine hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; b) aq. 3 N HCl, MeOH, rt; c) HCO_2Et, NaOMe, rt; d) $NH_2OH \cdot HCl$, AcOH, EtOH, heat; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 36



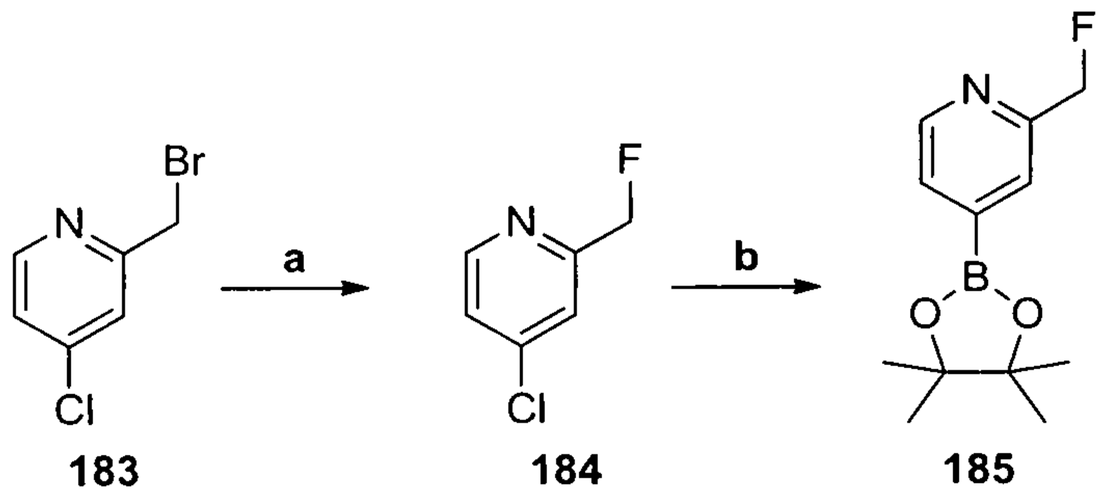
Reagents and conditions: a) i) 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-4-carboximidamide hydrochloride, K_2CO_3, EtOH, microwave, 120 °C; ii) DDQ, CH_2Cl_2, rt; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) K_2CO_3, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 37



Reagents and conditions: a) 2-F-PhB(OH)$_2$, Na_2CO_3, Pd(dppf)Cl_2, 1,4-dioxane, H_2O, 100 °C; b) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; c) K_2CO_3, MeOH, rt; d) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

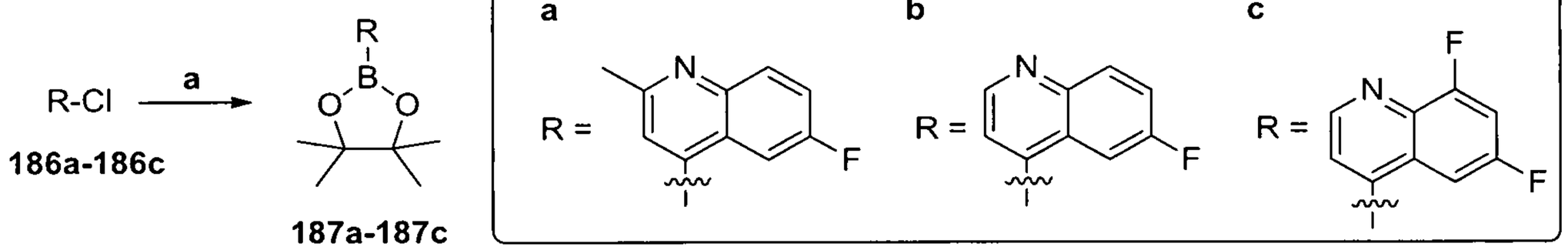
Scheme 38



183 **184** **185**

Reagents and conditions: a) TBAF·3H_2O, MeCN, rt; b) bis(pinacolato)diboron, KOAc, Pd(dppf)Cl_2, 1,4-dioxane, 130 °C.

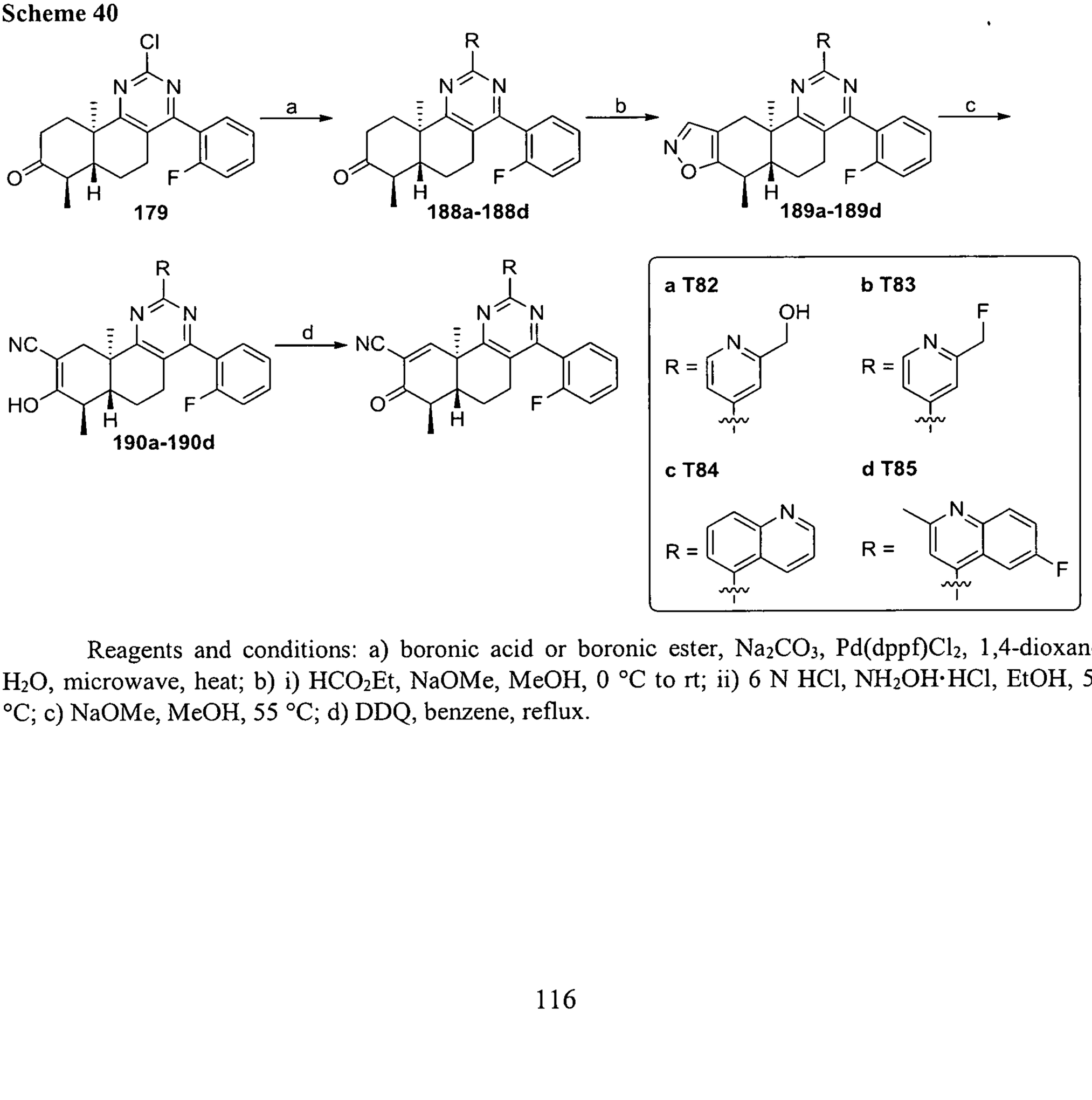
Scheme 39



186a-186c **187a-187c**

Reagents and conditions: a) bis(pinacolato)diboron, KOAc, Pd(dppf)Cl_2, 1,4-dioxane, 125 °C.

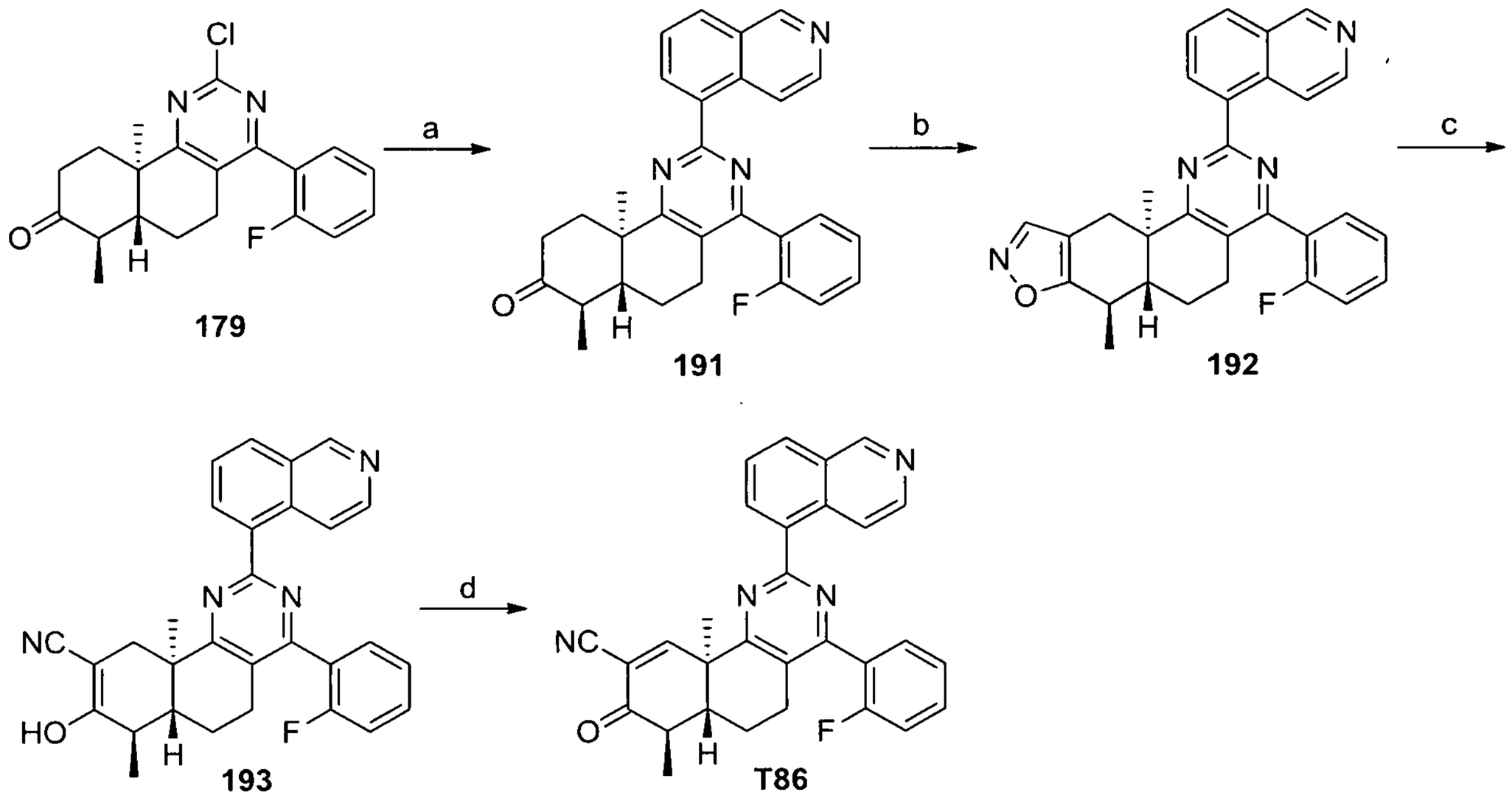
Scheme 40



179 **188a-188d** **189a-189d** **190a-190d**

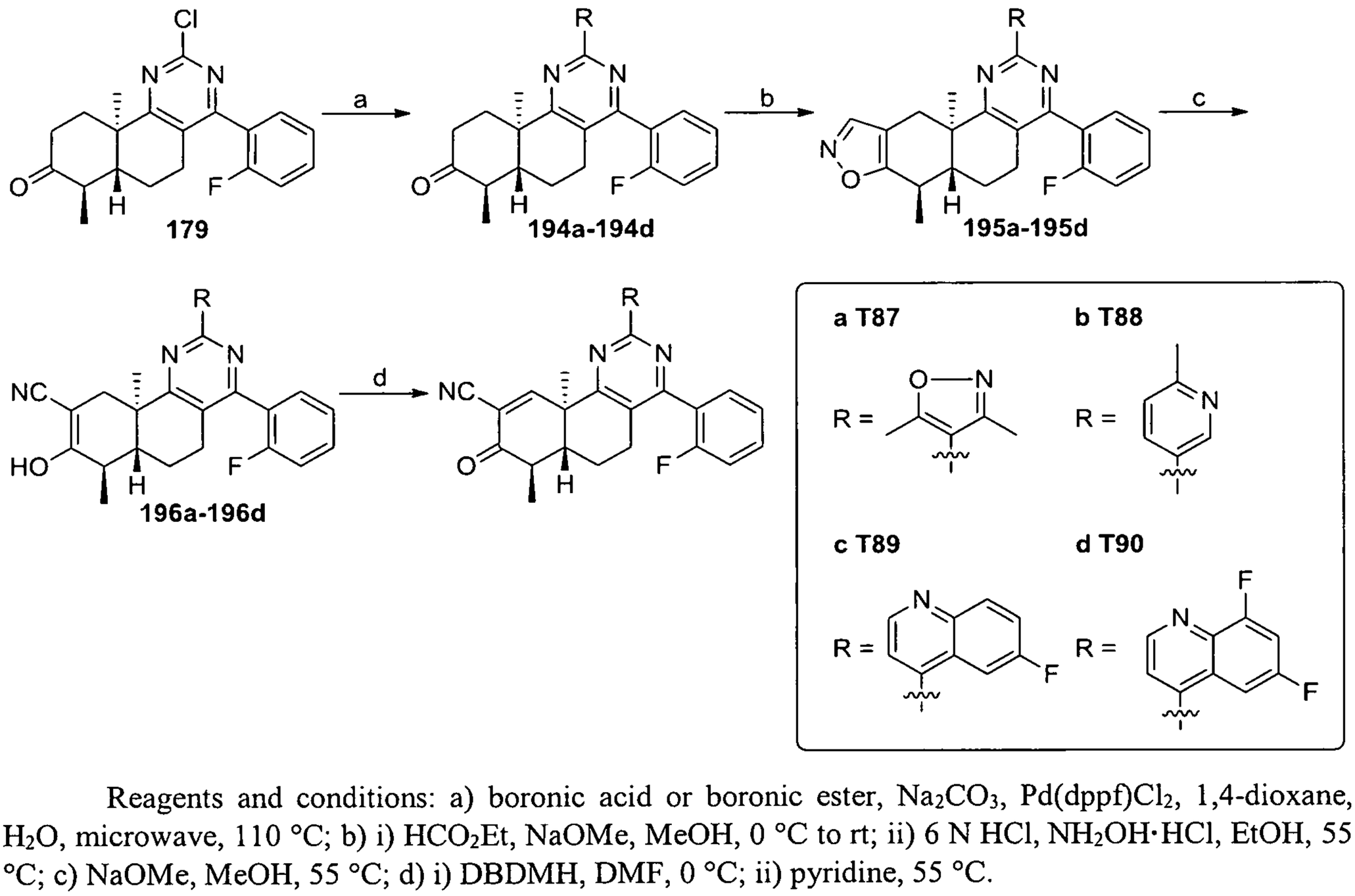
Reagents and conditions: a) boronic acid or boronic ester, Na_2CO_3, Pd(dppf)Cl_2, 1,4-dioxane, H_2O, microwave, heat; b) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, NH_2OH·HCl, EtOH, 55 °C; c) NaOMe, MeOH, 55 °C; d) DDQ, benzene, reflux.

Scheme 41



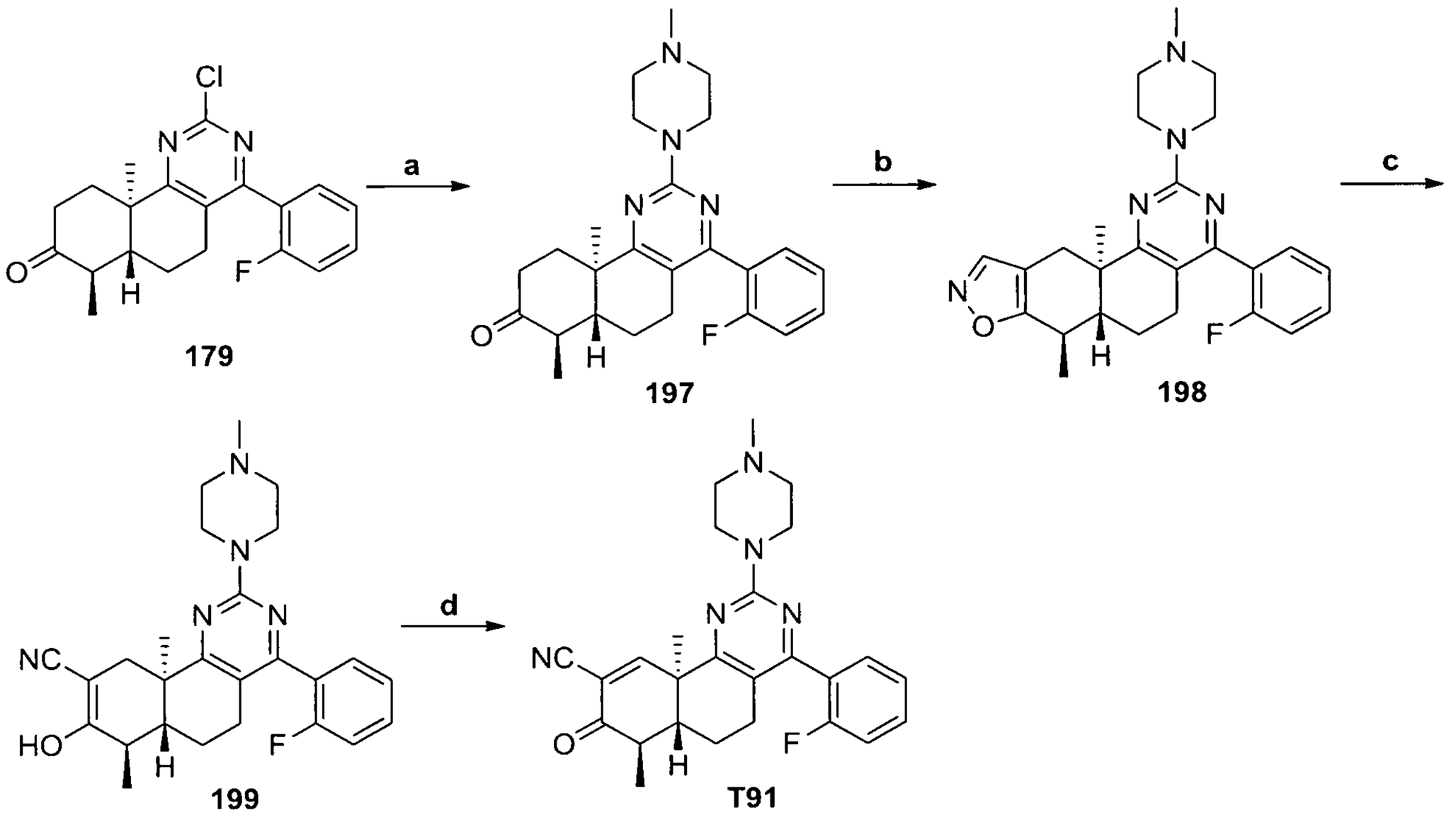
Reagents and conditions: a) isoquinoline-5-boronic acid, Na_2CO_3, $Pd(dppf)Cl_2$, 1,4-dioxane, H_2O, microwave, 110 °C; b) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; c) K_2CO_3, MeOH, rt; d) DDQ, benzene, 85 °C.

Scheme 42



Reagents and conditions: a) boronic acid or boronic ester, Na_2CO_3, $Pd(dppf)Cl_2$, 1,4-dioxane, H_2O, microwave, 110 °C; b) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; c) NaOMe, MeOH, 55 °C; d) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 43

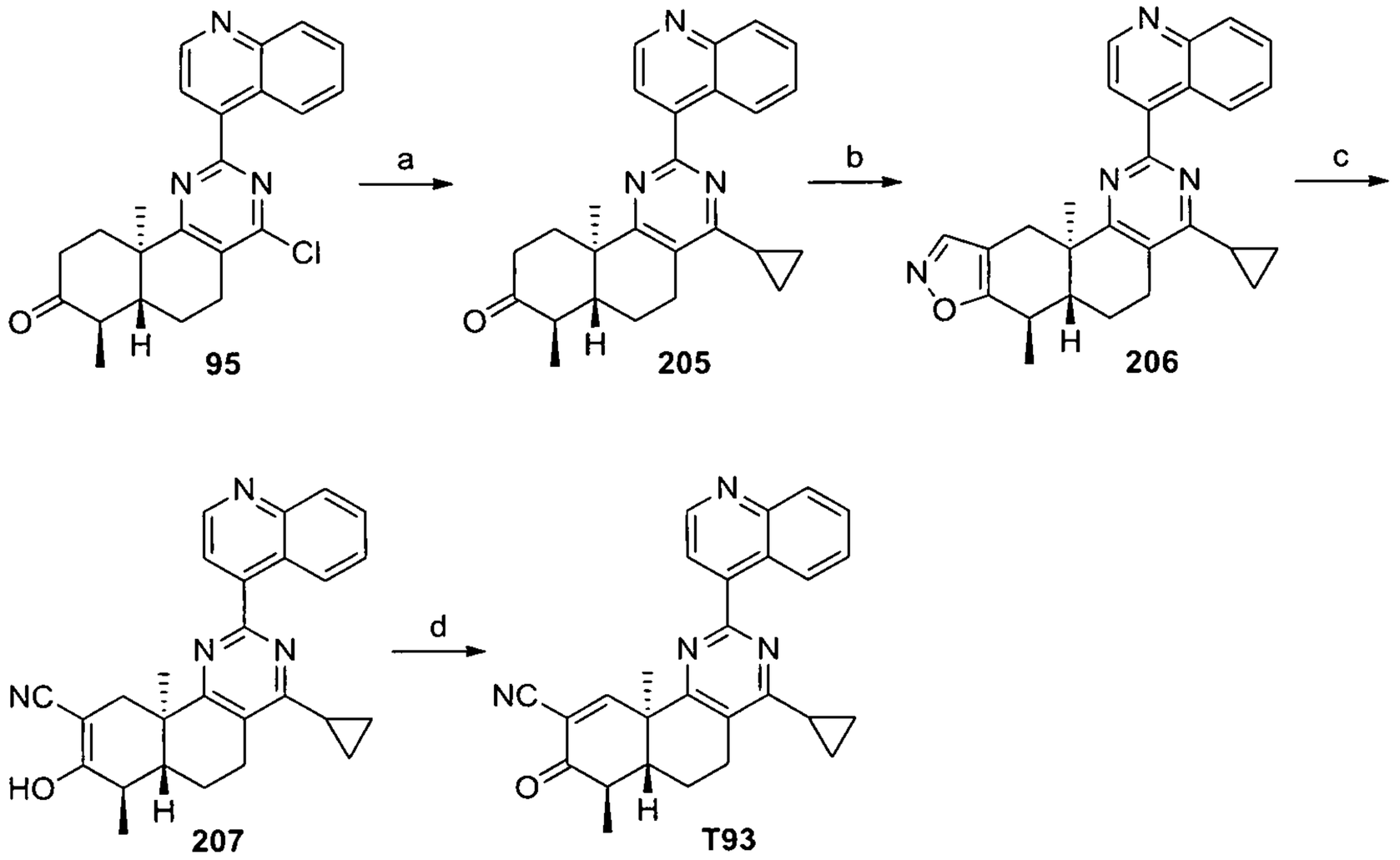


Reagents and conditions: a) 1-methylpiperazine, NMP, 100 °C; b) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; c) K_2CO_3, MeOH, rt; d) DDQ, benzene, 85 °C.

Scheme 44

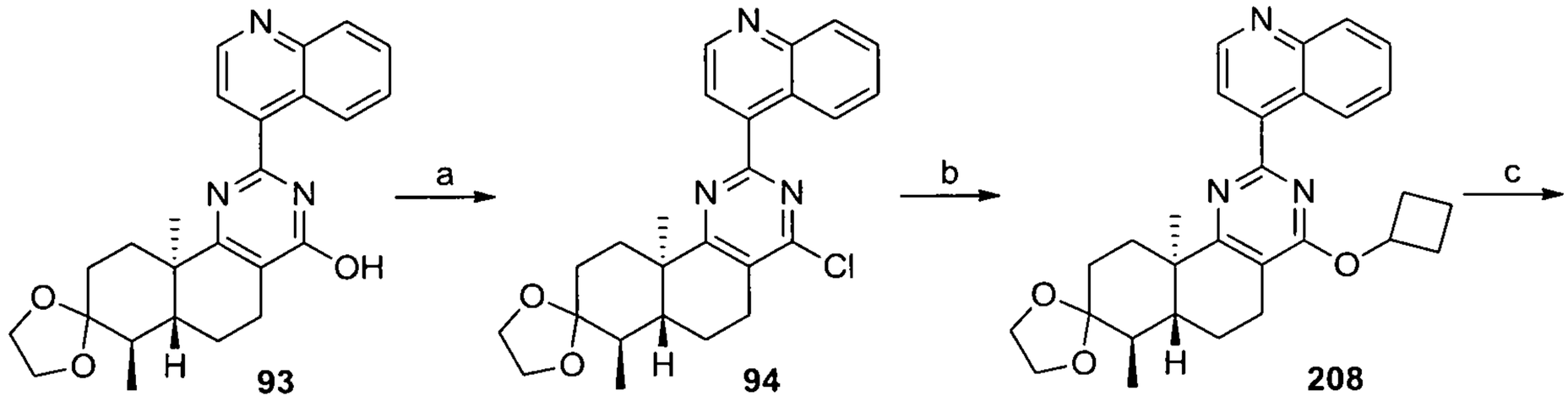
Reagents and conditions: a) i) *N*-amidinomorpholine hydrobromide, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; b) aq. 3 N HCl, THF, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH{\cdot}HCl$, HOAc, EtOH, 60 °C-rt; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, DMF, 60 °C.

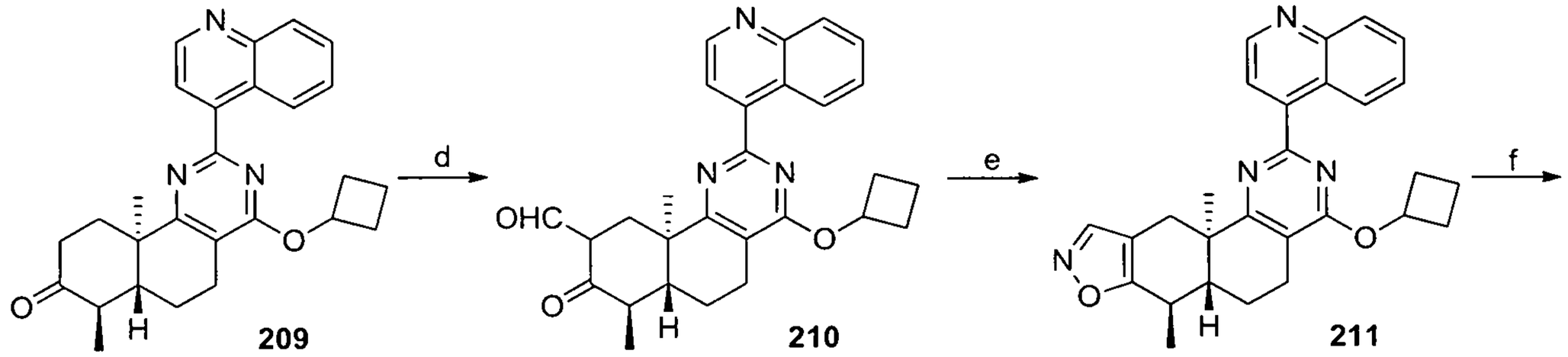
Scheme 45

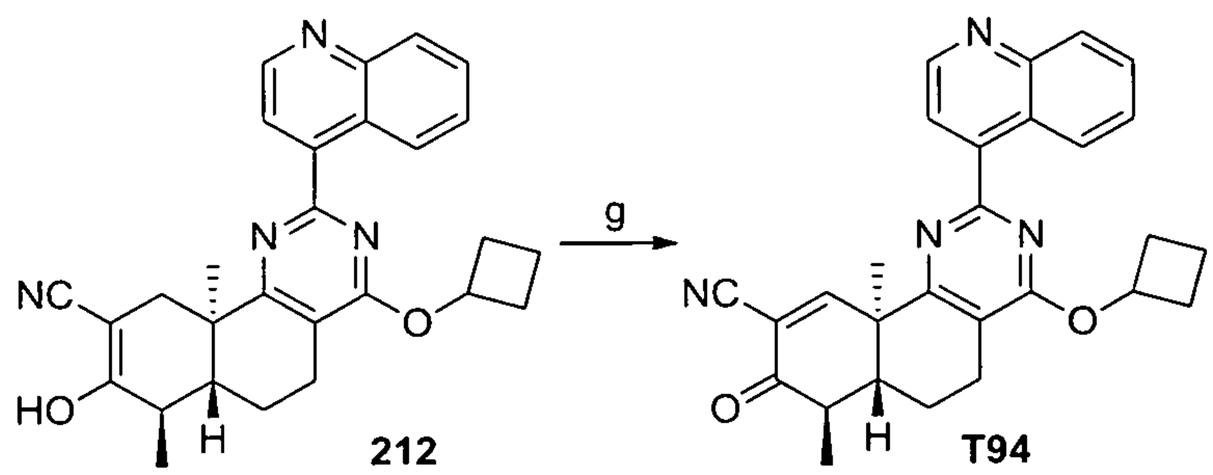


Reagents and conditions: a) cyclopropylboronic acid, K_3PO_4, $Pd(OAc)_2$, tricyclohexylphosphine, toluene, H_2O, microwave, 130 °C; b) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; c) NaOMe, MeOH, 55 °C; d) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 46

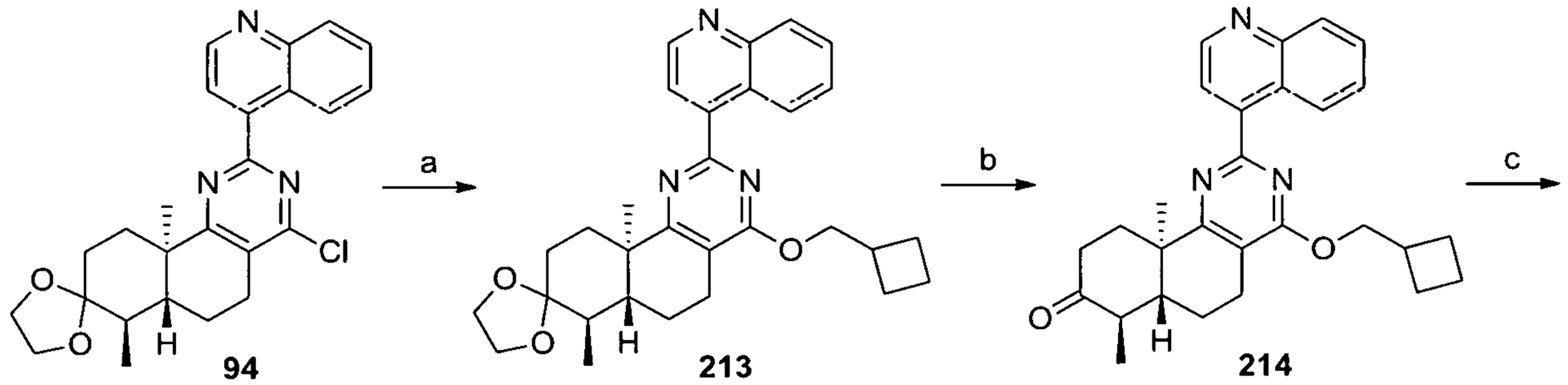


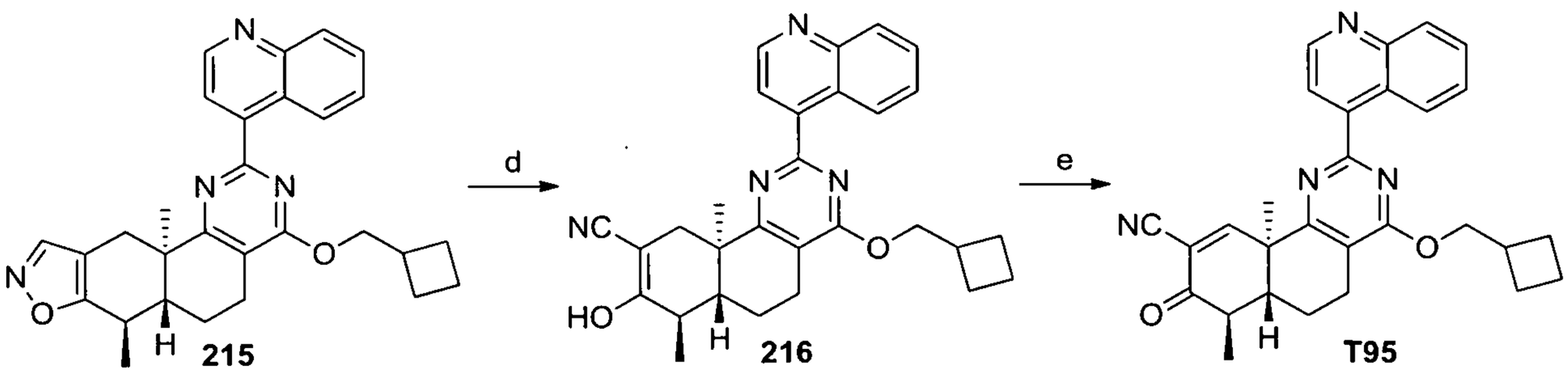




Reagents and conditions: a) i) $POCl_3$, toluene, microwave, 100 °C; ii) ethylene glycol, $TsOH \cdot H_2O$, benzene, reflux, $-H_2O$; b) cyclobutanol, NaH, THF, 60 °C; c) aq. 3 N HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, AcOH, EtOH, 50 °C; f) K_2CO_3, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

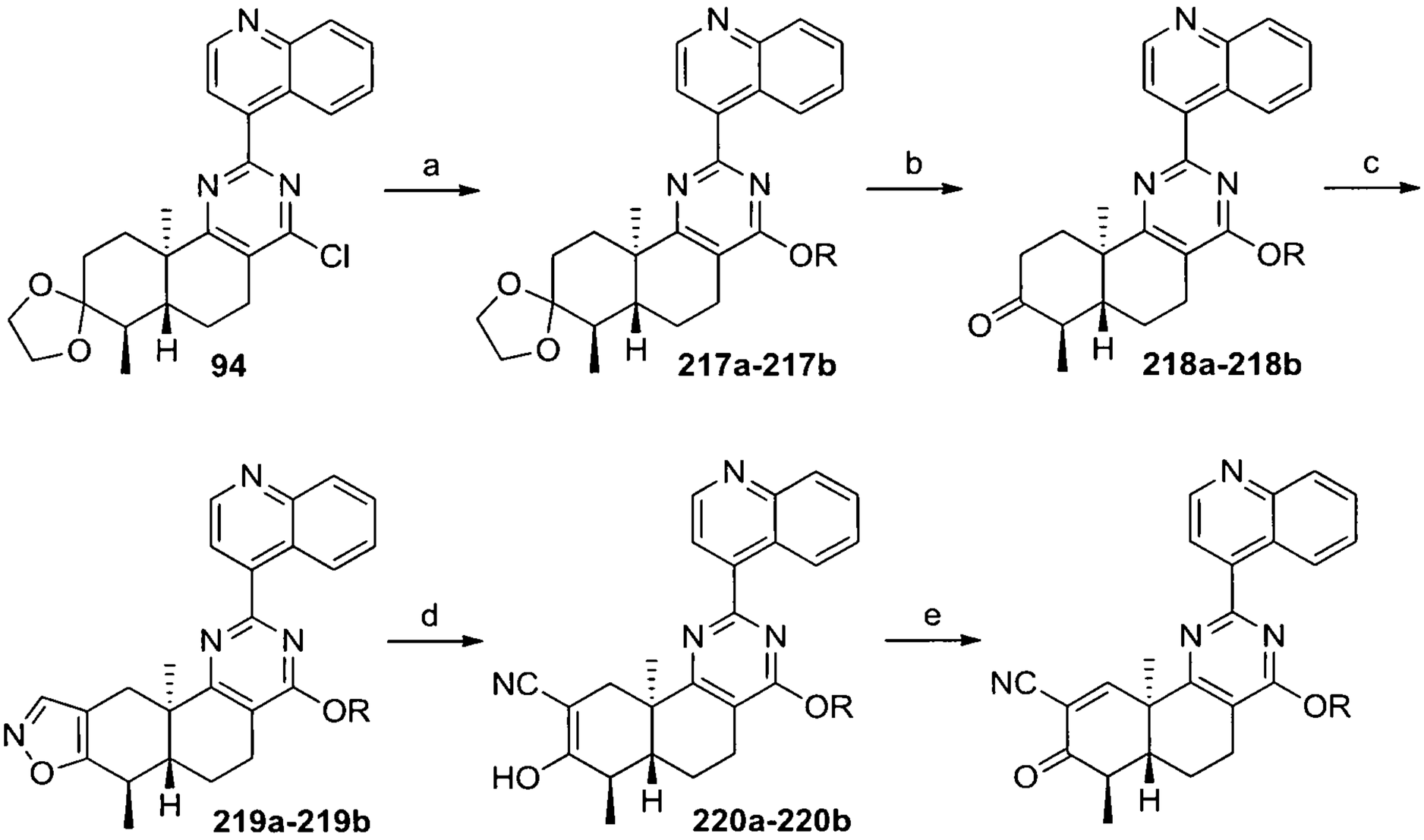
Scheme 47





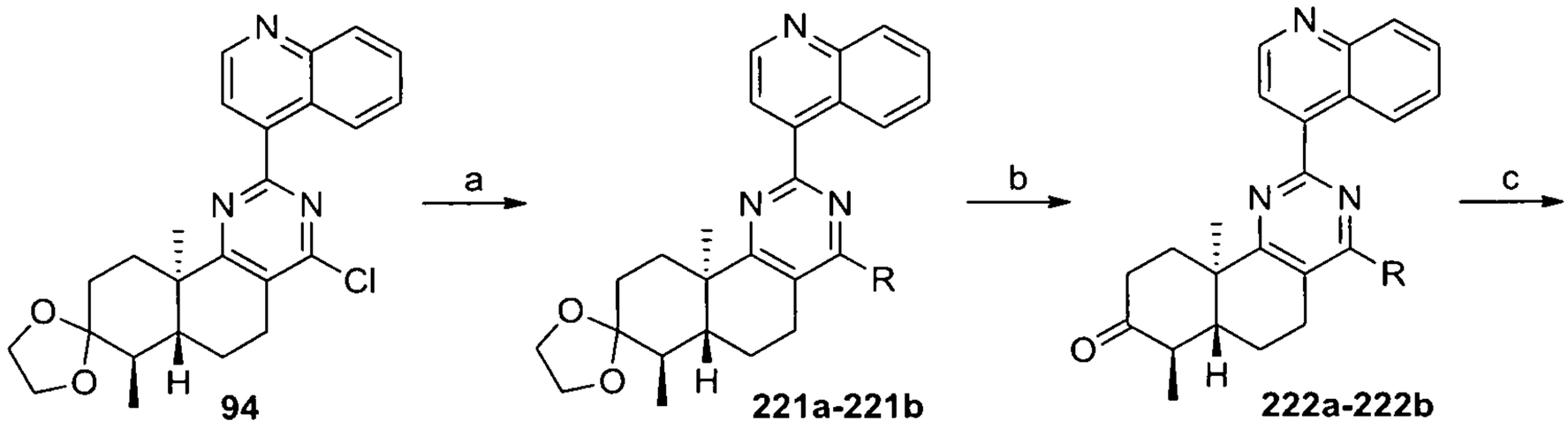
Reagents and conditions: a) cyclobutanemethanol, NaH, THF, rt to 50 °C; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; d) K_2CO_3, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 48



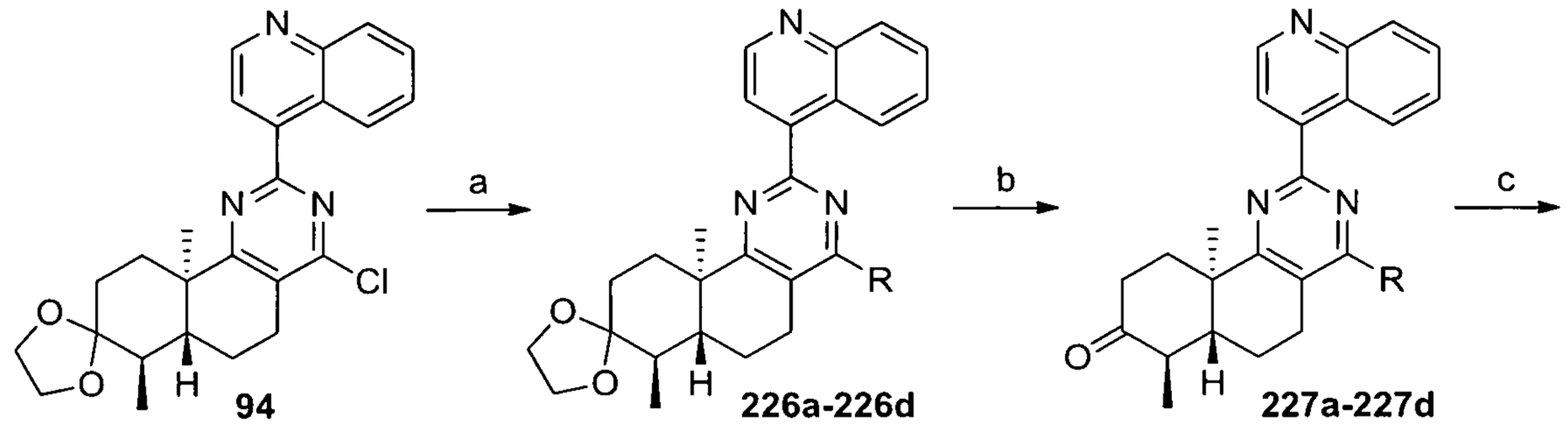
Reagents and conditions: a) ROH, NaH, THF, rt to 50 °C; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 49



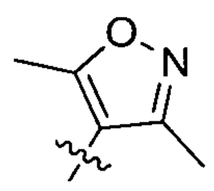
Reagents and conditions: a) $MeSO_2NH_2$, NaH, DMF, 80 °C; b) aq. 3 N HCl, THF, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH \cdot HCl$, EtOH, AcOH, 50 °C; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 50



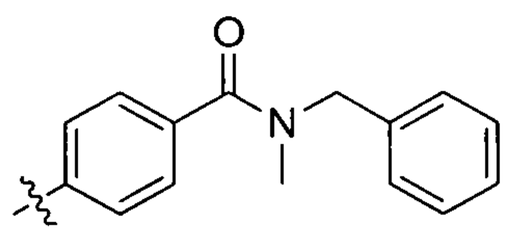
a T100

R =



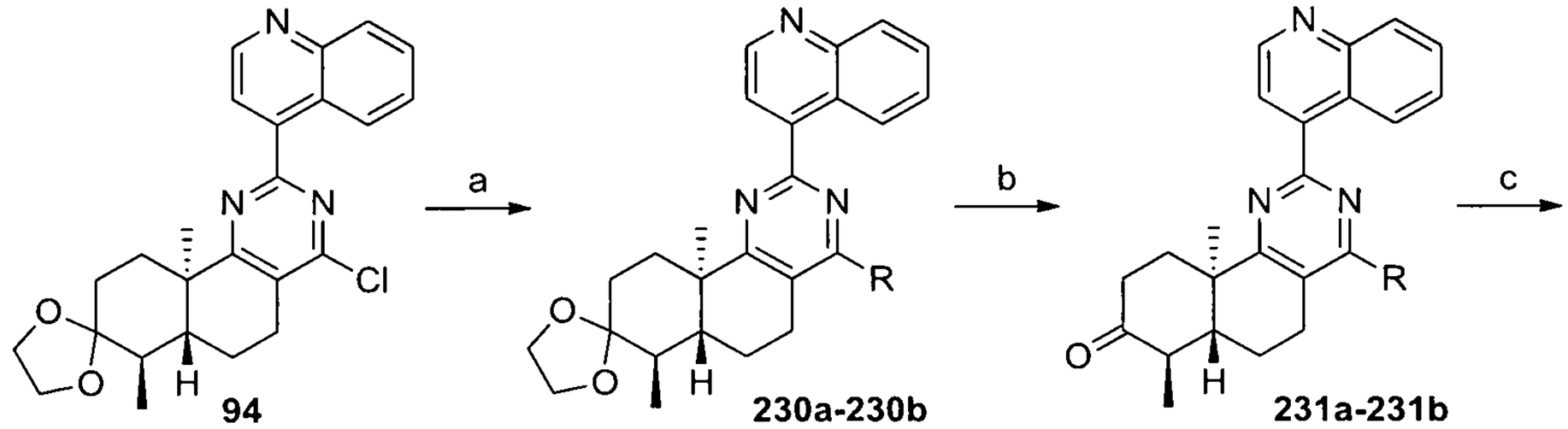
b T101

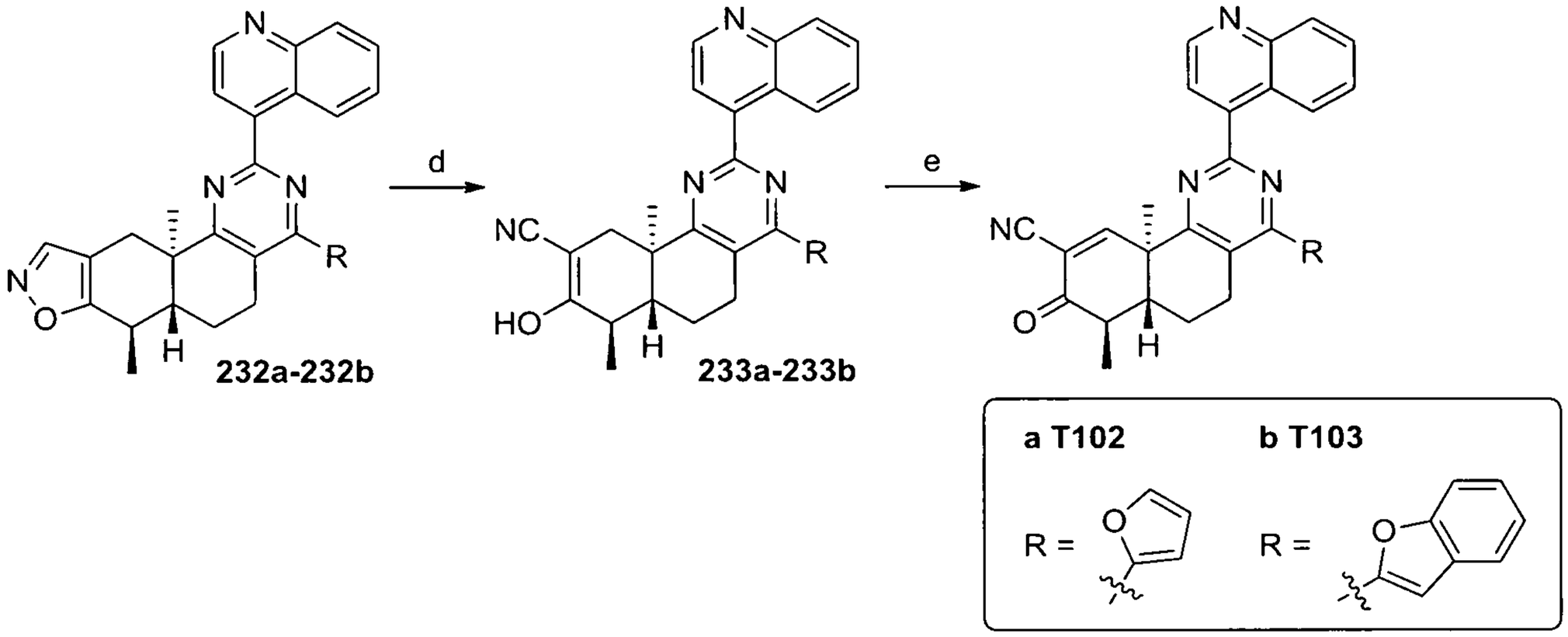
R =



Reagents and conditions: a) boronic acid or boronic ester, $Pd(dppf)Cl_2$, Na_2CO_3, 1,4-dioxane, H_2O, 110 °C, microwave; b) aq. 3 N HCl, MeOH, THF, rt; c) i) HCO_2Et, NaOMe, MeOH, rt; ii) aq. 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

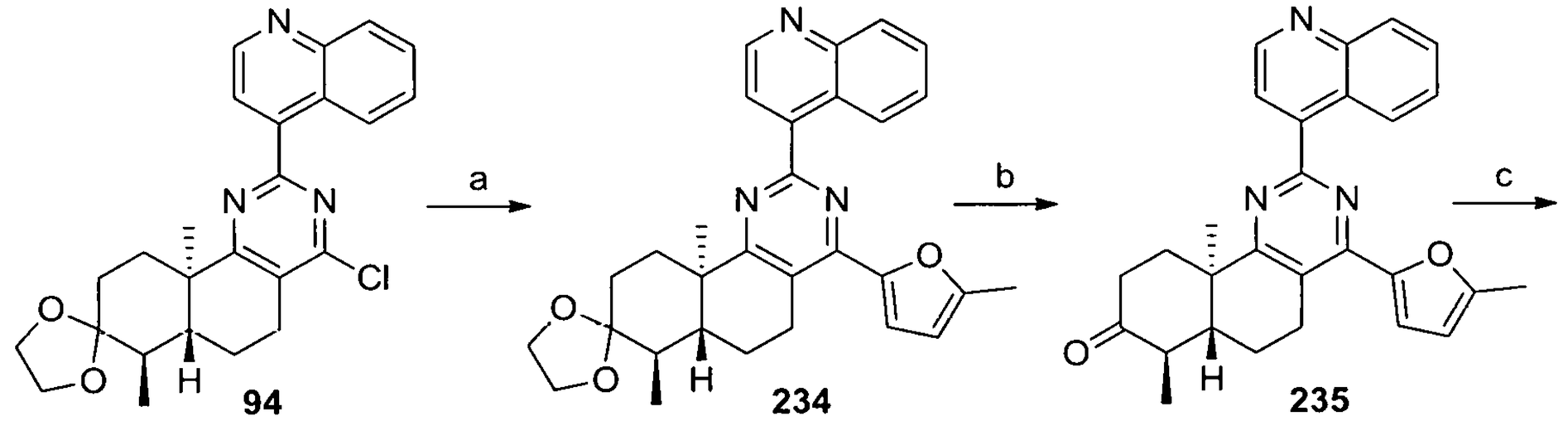
Scheme 51

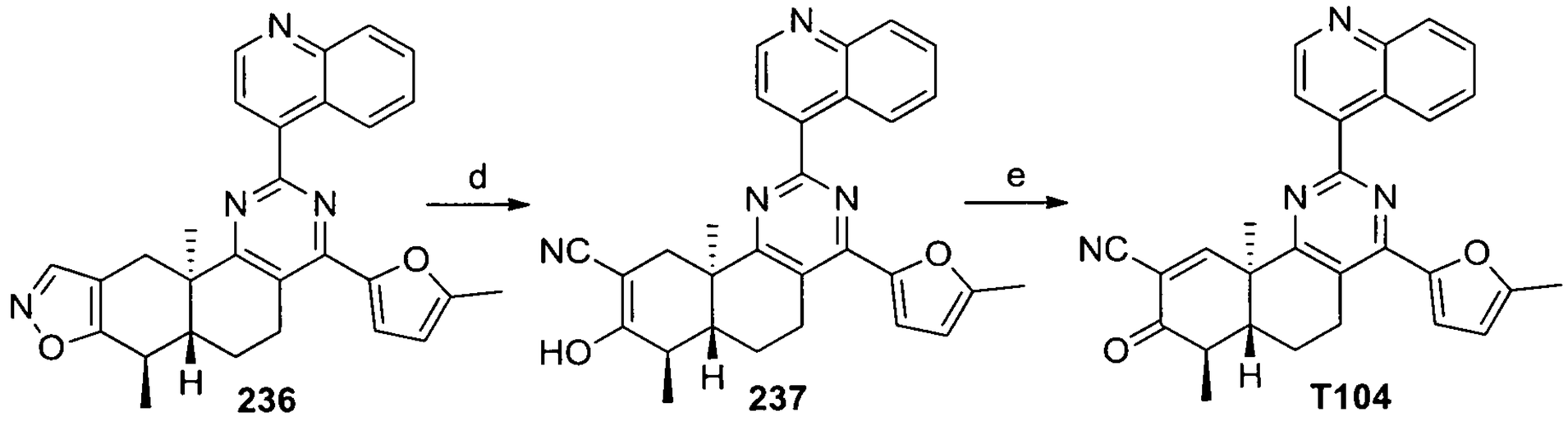




Reagents and conditions: a) boronic acid, $Pd(dppf)Cl_2$, Na_2CO_3, 1,4-dioxane, H_2O, 110 °C, microwave; b) aq. 3 N HCl, MeOH, THF, rt; c) i) HCO_2Et, NaOMe, MeOH, rt; ii) aq. 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) DDQ, benzene, reflux.

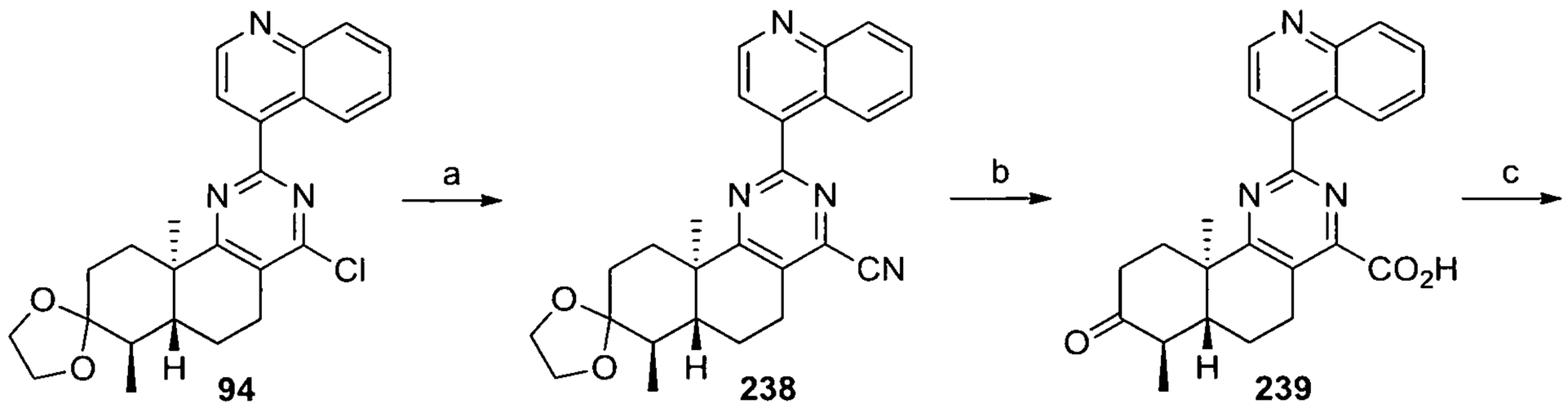
Scheme 52





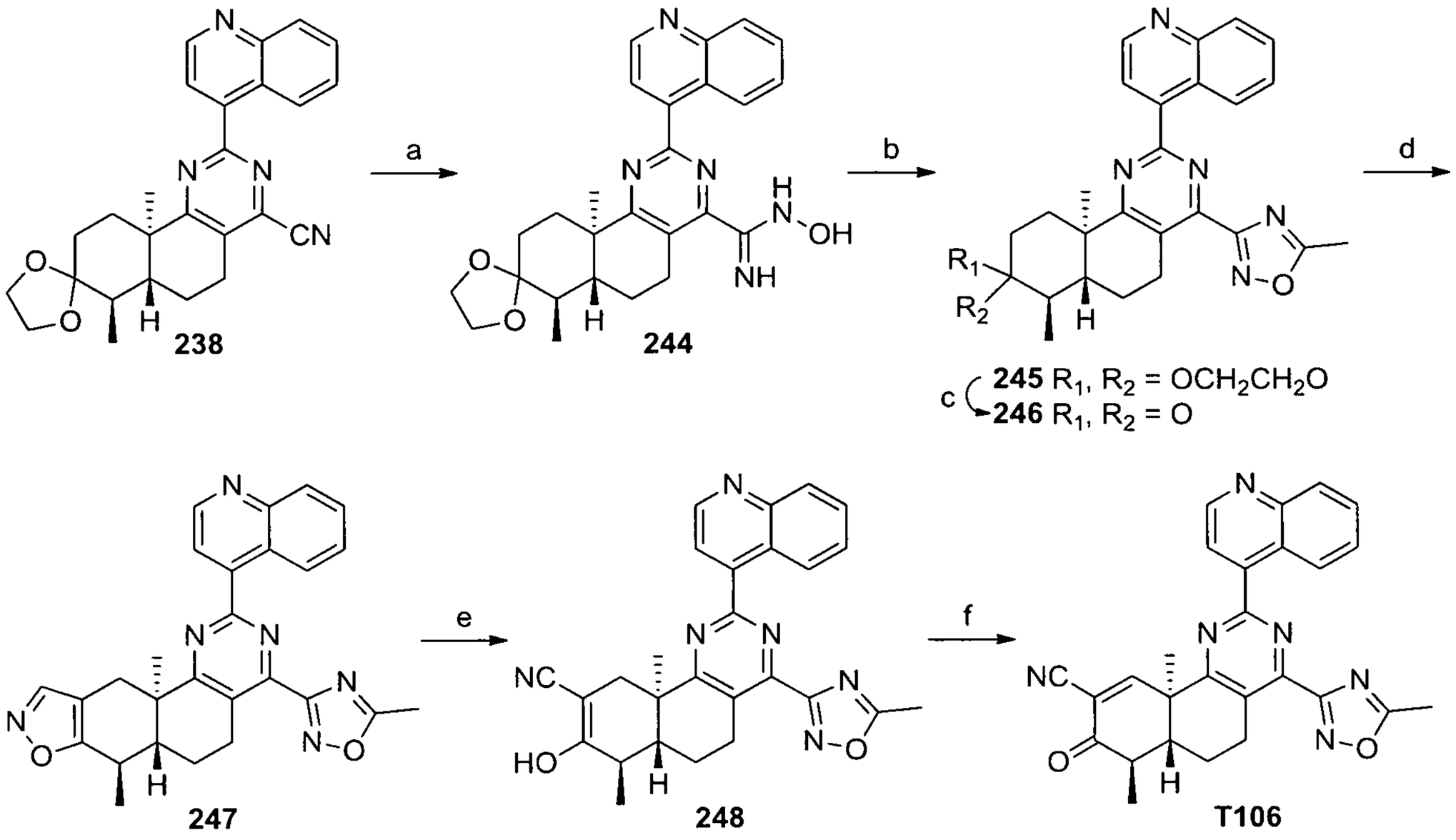
Reagents and conditions: a) 5-methyl-2-furanboronic acid pinacol ester, $Pd(dppf)Cl_2$, Na_2CO_3, 110 °C, microwave; b) aq. 3 N HCl, MeOH, THF, rt; c) i) HCO_2Et, NaOMe, MeOH, rt; ii) aq. 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 53



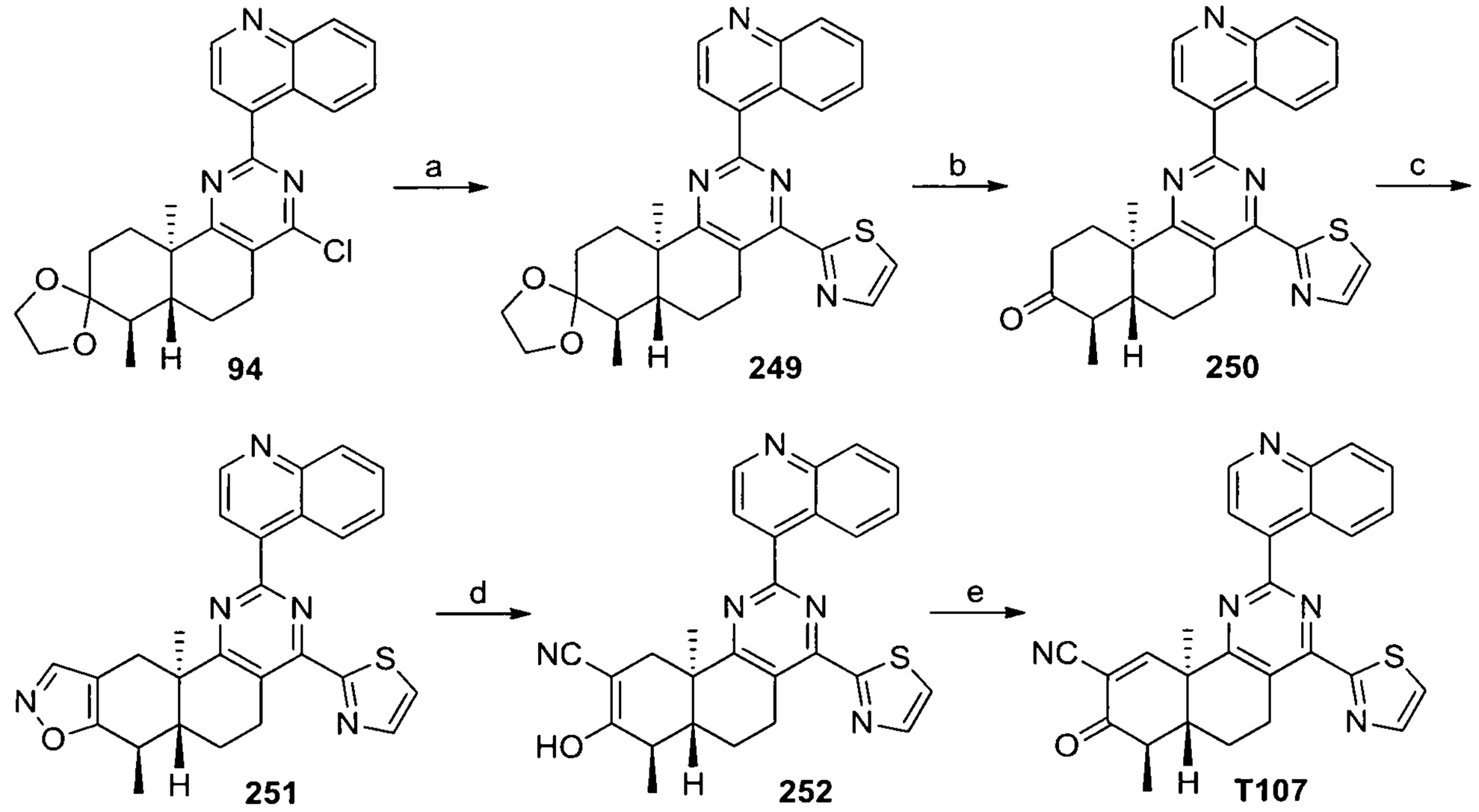
Reagents and conditions: a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMA, 120 °C; b) aq. H_2SO_4, 100 °C; c) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; d) i) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C-rt; ii) acetamide oxime, Et_3N, CH_2Cl_2, 0 °C-rt; e) toluene, reflux, $-H_2O$; f) K_2CO_3, MeOH, rt; g) DDQ, benzene, 85 °C.

Scheme 54



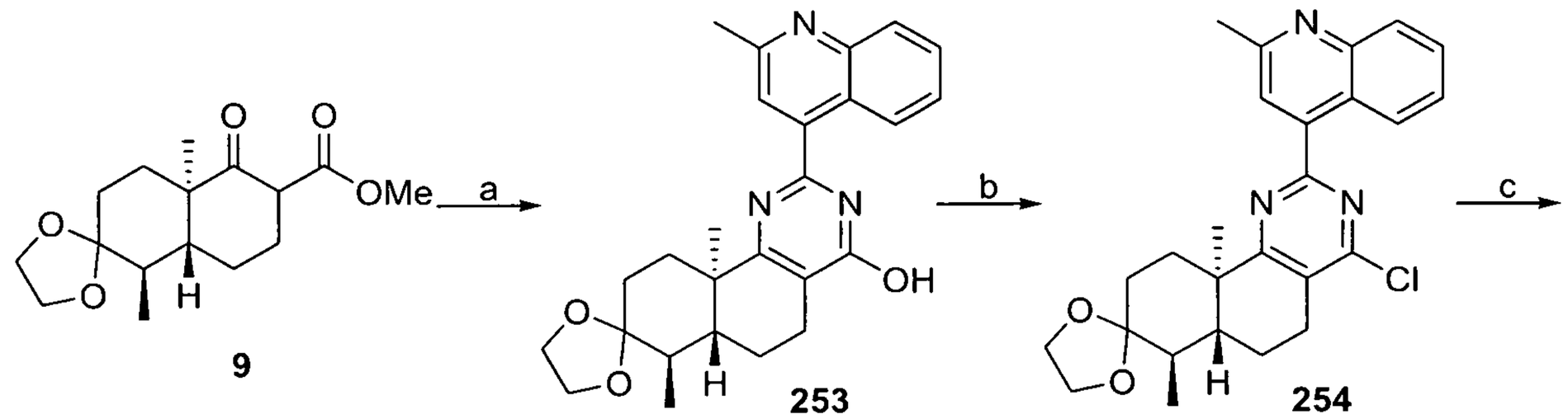
Reagents and conditions: a) $NH_2OH{\cdot}HCl$, $NaHCO_3$, EtOH, reflux to rt; b) Ac_2O, AcOH, rt to 100 °C; c) aq. 3 N HCl, MeOH, rt; d) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; e) K_2CO_3, MeOH; f) DDQ, benzene, 85 °C.

Scheme 55



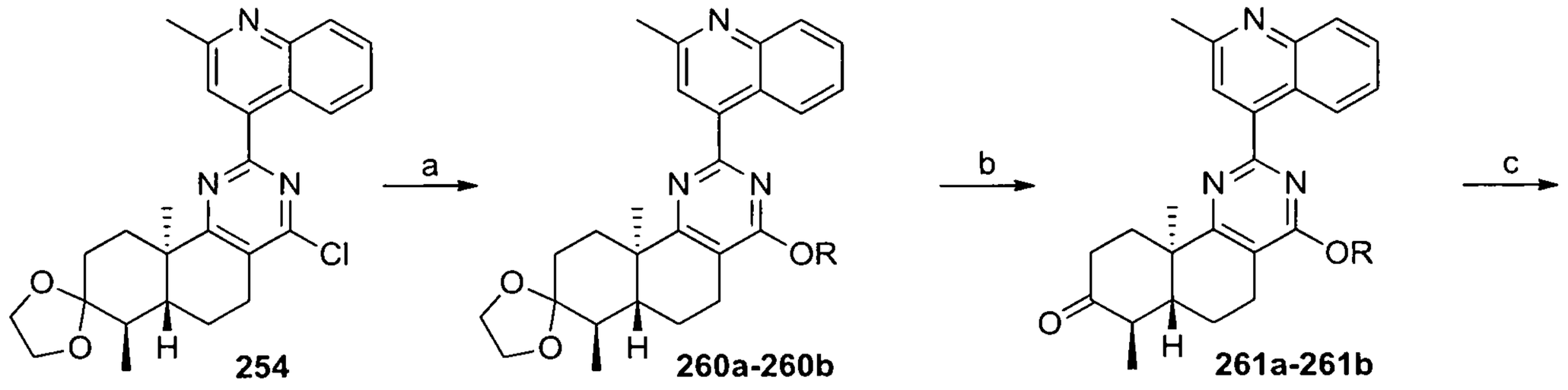
Reagents and conditions: a) 2-(tri-*n*-butylstannyl)thiazole, $Pd(PPh_3)_4$, 1,4-dioxane, reflux; b) aq. 3 N HCl, MeOH, THF, rt; c) i) HCO_2Et, NaOMe, MeOH, 0 °C-rt; ii) aq. 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) K_2CO_3, MeOH, rt; e) DDQ, benzene, reflux.

Scheme 56



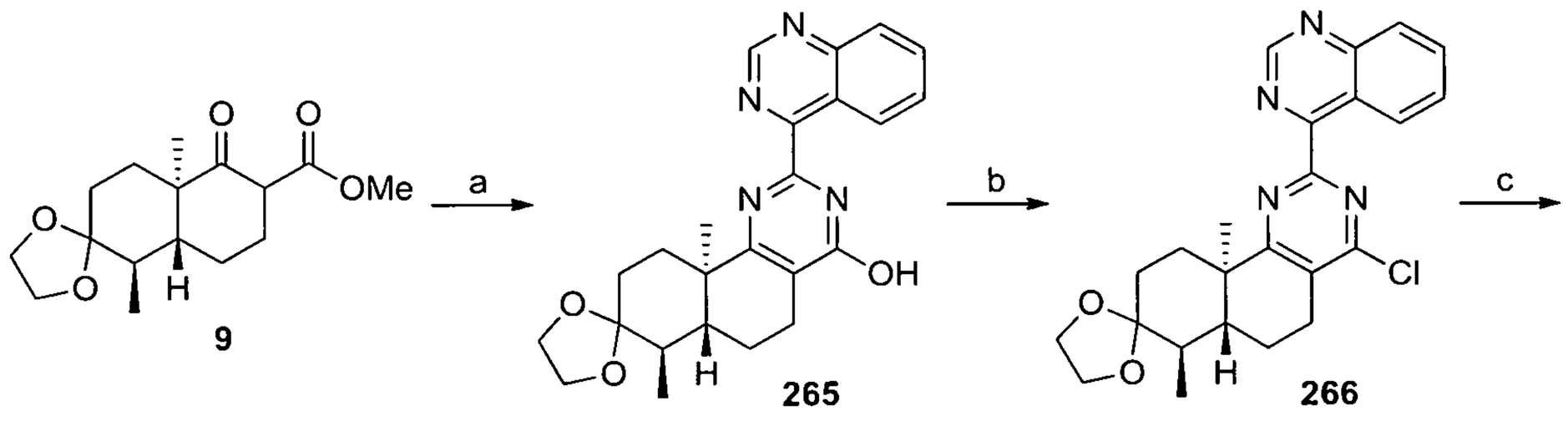
Reagents and conditions: a) 2-methyl-4-quinolinecarboximidamide hydrochloride, K_2CO_3, EtOH, 40 °C; b) i) $POCl_3$, toluene, microwave, 100 °C; ii) ethylene glycol, $TsOH \cdot H_2O$, benzene, reflux, $-H_2O$; c) $RB(OH)_2$, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, 90 °C; d) aq. 3 N HCl, MeOH, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, EtOH, 60 °C-rt; g) K_2CO_3, MeOH, rt; h) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 57



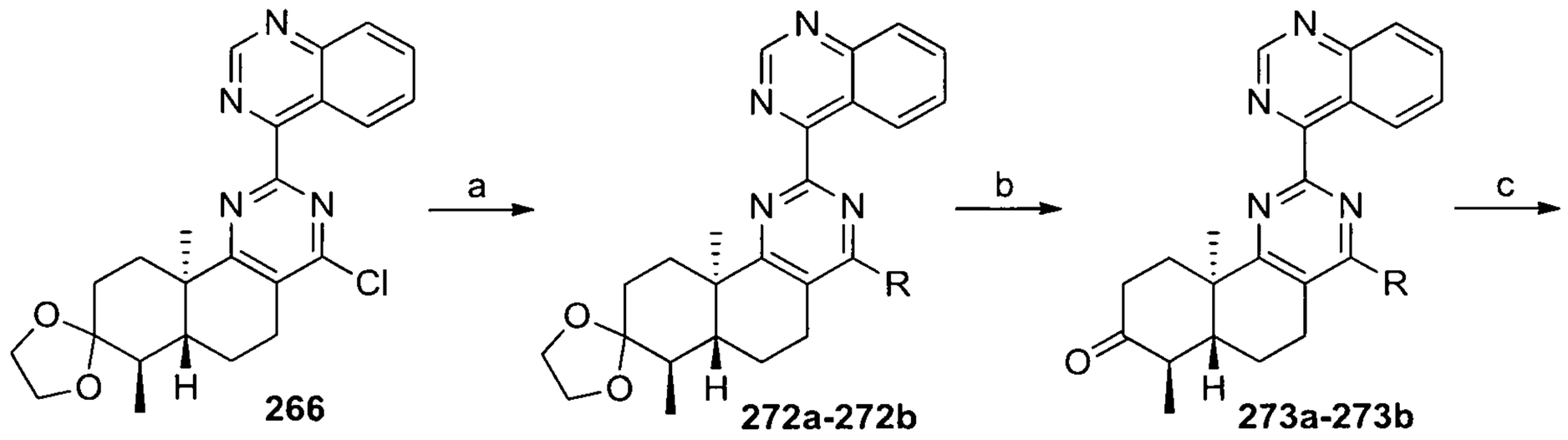
Reagents and conditions: a) ROH, NaH, THF, 60 °C; b) aq. 3 N HCl, MeOH, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH \cdot HCl$, AcOH, EtOH, heat; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; or Br_2, CH_2Cl_2, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 58



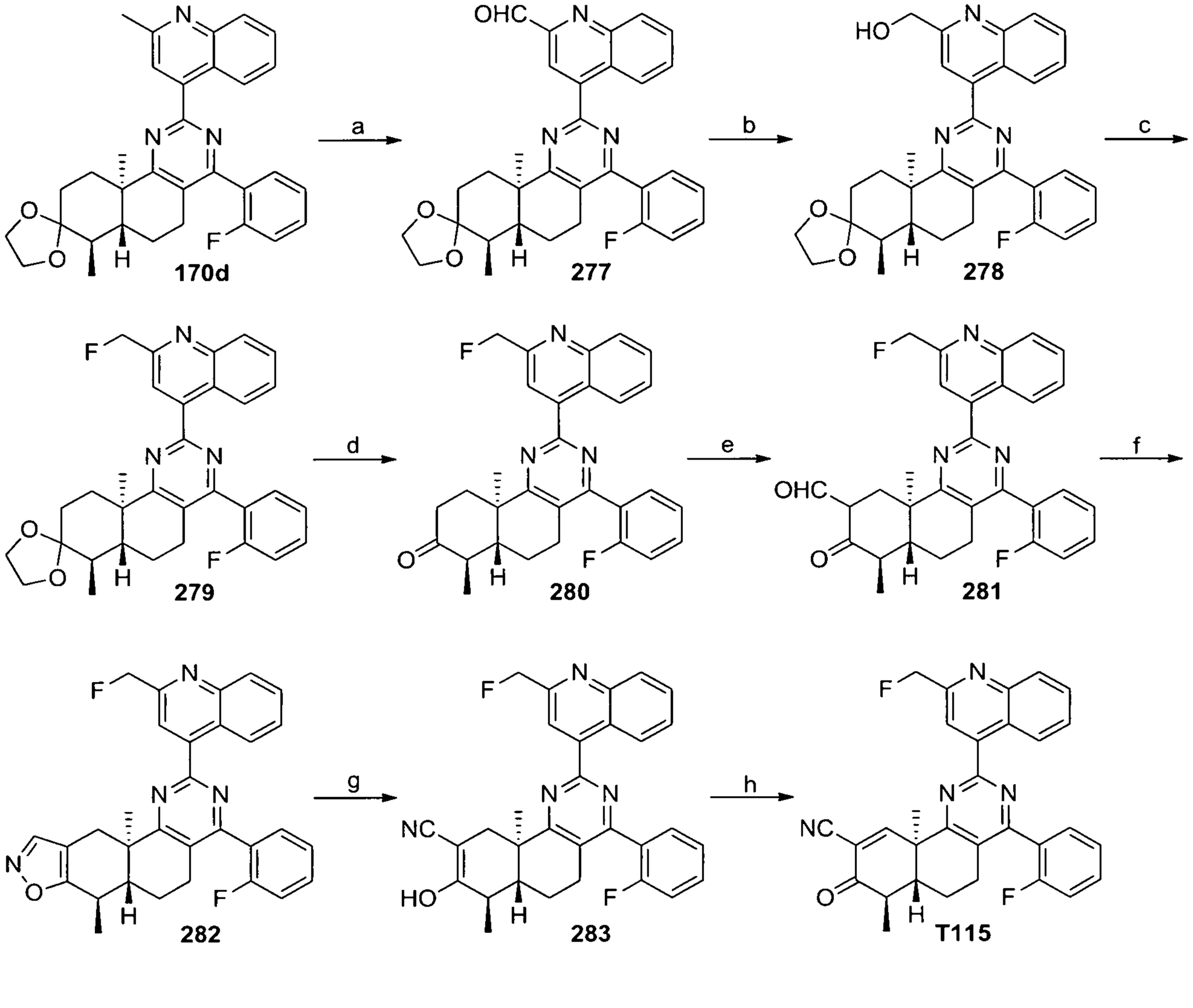
Reagents and conditions: a) Quinazoline-4-carboximidamide hydrochloride, K_2CO_3, EtOH, 40 °C; b) i) $POCl_3$, toluene, microwave, 100 °C; ii) ethylene glycol, $TsOH \cdot H_2O$, benzene, reflux, $-H_2O$; c) cyclobutanol, NaH, THF, 60 °C; d) aq. 3 N HCl, THF, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, AcOH, EtOH, 50 °C; g) K_2CO_3, MeOH, rt; h) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 59



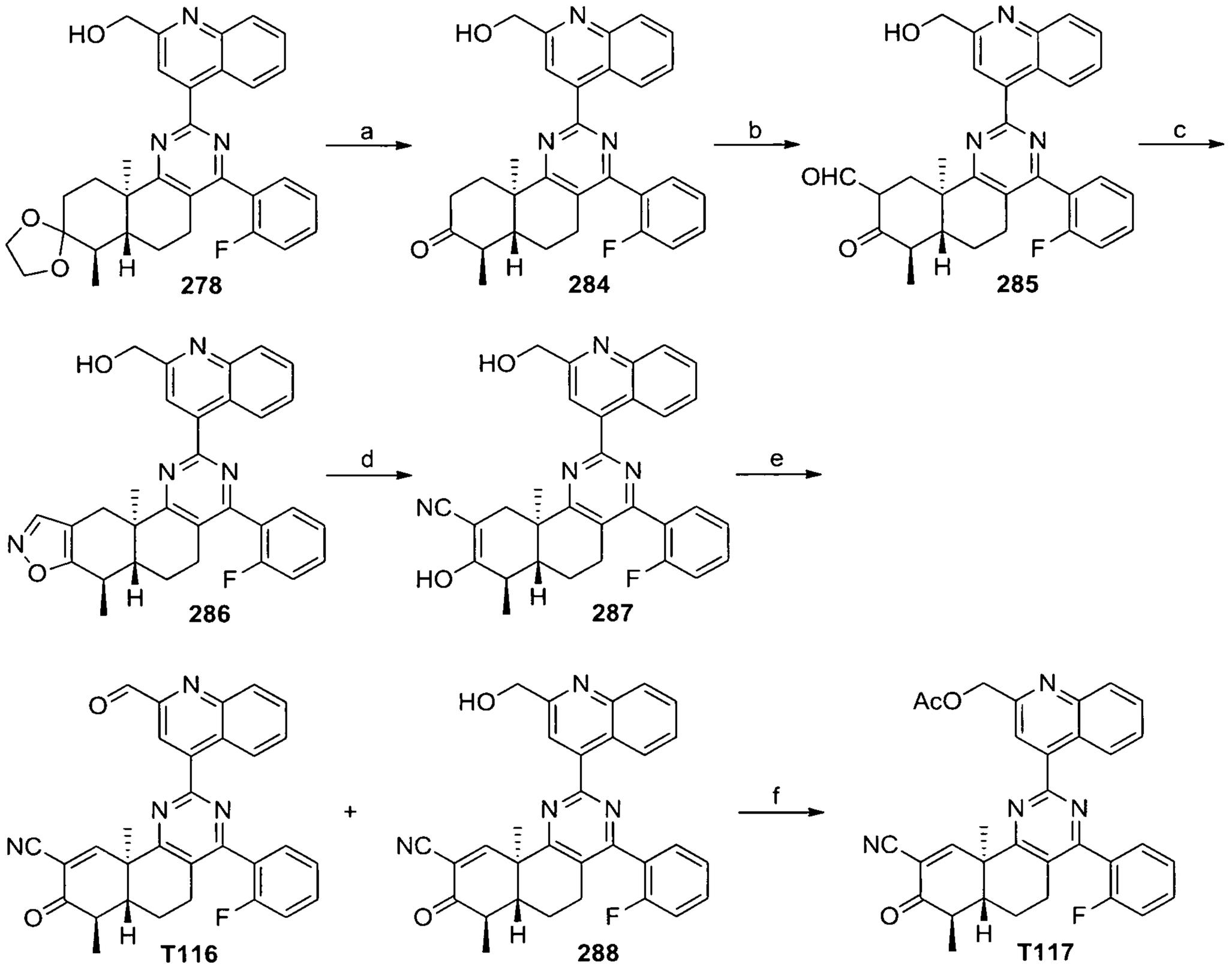
Reagents and conditions: a) $RB(OH)_2$, K_2CO_3, $Pd(dppf)_2Cl_2$, 1,4-dioxane, 90 °C; b) aq. 3 N HCl, THF, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH \cdot HCl$, AcOH, EtOH, 50 °C; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 60



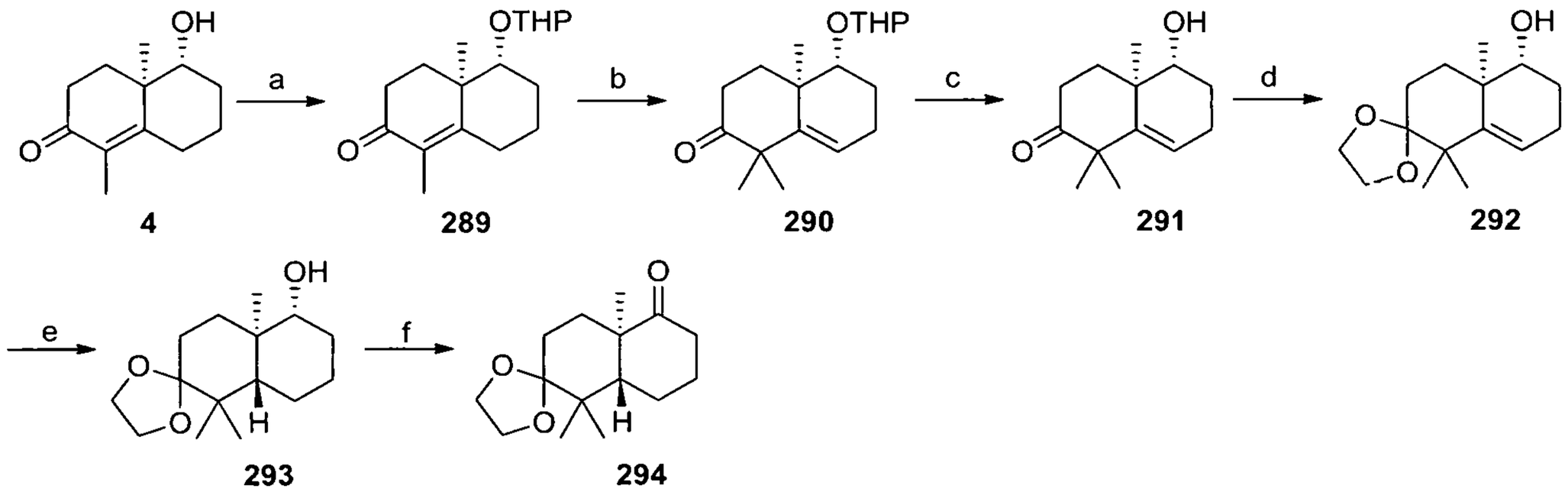
Reagents and conditions: a) SeO_2, 1,4-dioxane, 100 °C; b) $NaBH_4$, EtOH, rt; c) DAST, CH_2Cl_2, 0 °C; d) aq. 3 N HCl, MeOH, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, HOAc, EtOH, 60 °C-rt; g) K_2CO_3, MeOH, rt; h) i) DBDMH, DMF, 0 °C; ii) pyridine, DMF, 60 °C.

Scheme 61



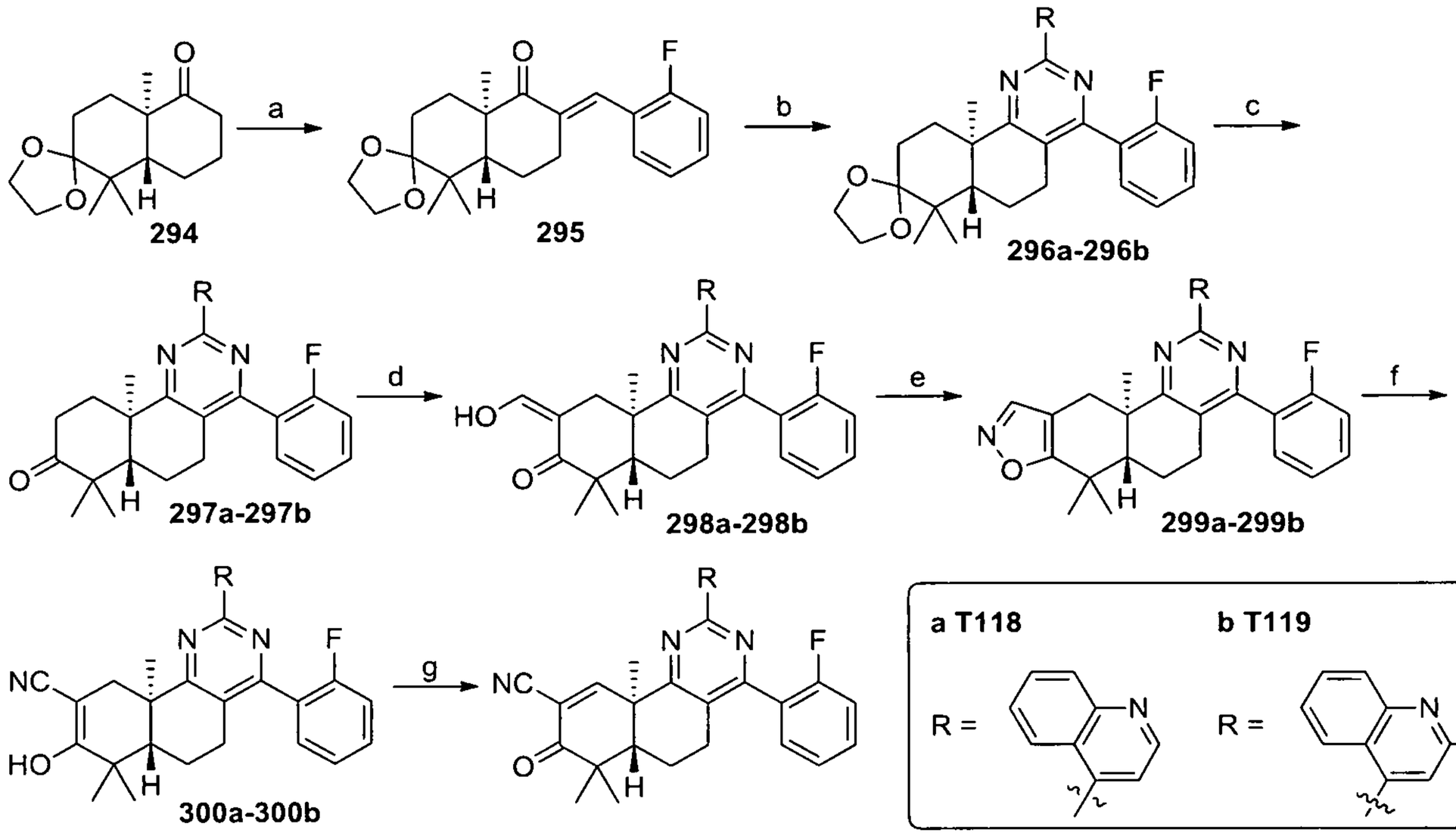
Reagents and conditions: a) aq. 3 N HCl, MeOH, rt; b) HCO_2Et, NaOMe, MeOH, rt; c) $NH_2OH{\cdot}HCl$, HOAc, EtOH, 60 °C to rt; d) K_2CO_3, MeOH, rt; e) DDQ, benzene, 80 °C; f) NaOAc, Ac_2O, rt.

Scheme 62



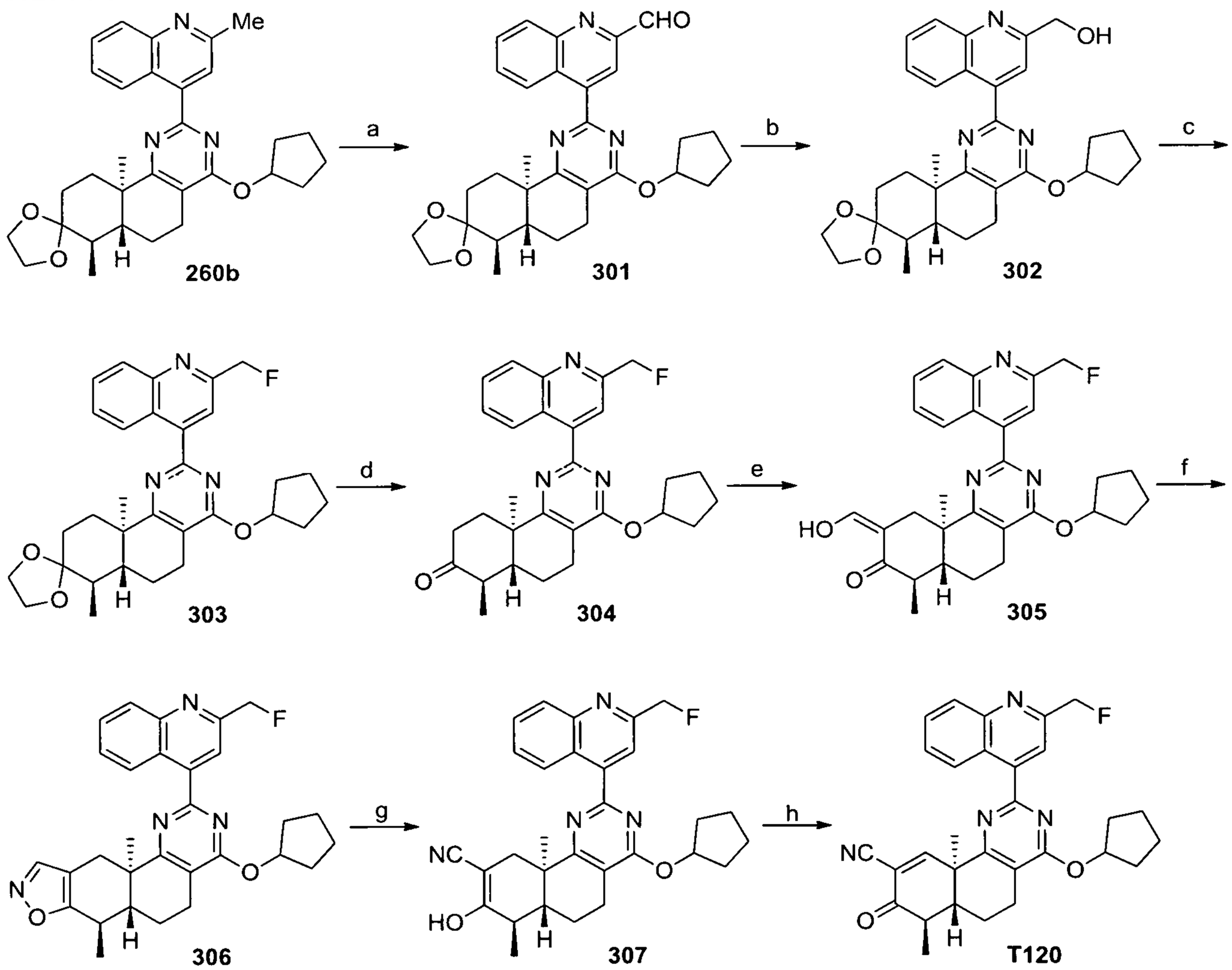
Reagents and conditions: a) 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2, rt; b) i) *t*-BuOK, benzene, rt-60 °C; ii) MeI, 0 °C-rt; c) PPTS, EtOH, reflux; d) ethylene glycol, *p*-TsOH, benzene, reflux, $-H_2O$; e) i) H_2, $Pd(OH)_2$ on C, MeOH, rt; ii) ethylene glycol, *p*-TsOH, benzene, reflux, $-H_2O$; f) PDC, $MgSO_4$, CH_2Cl_2, rt.

Scheme 63



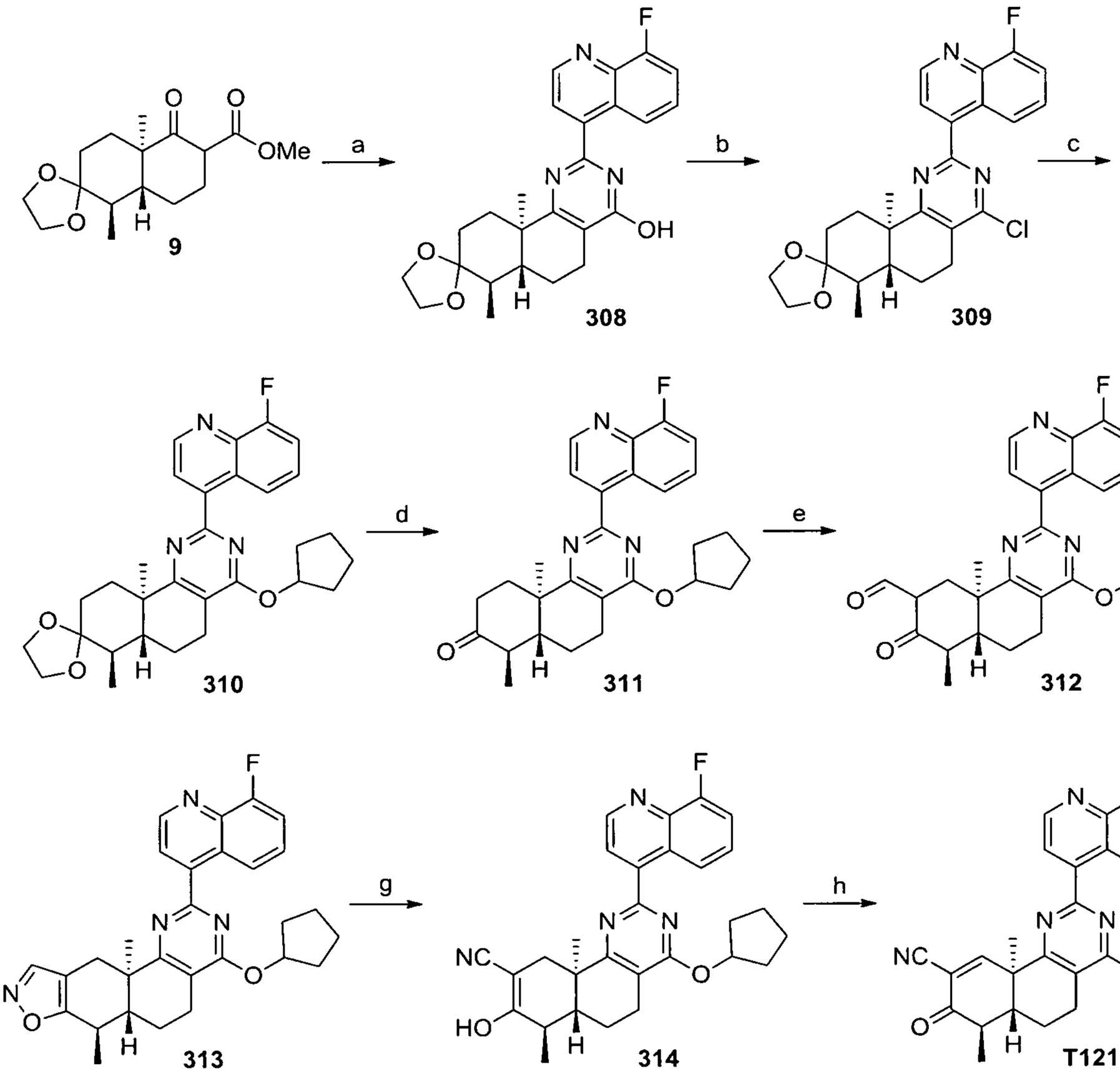
Reagents and conditions: a) 2-fluorobenzaldehyde, KF/Al_2O_3, EtOH, rt; b) i) $RC(NH)NH_2 \cdot HCl$, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; c) aq. HCl, MeOH, rt; d) HCO_2Et, NaOMe, rt; e) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C-rt; f) K_2CO_3, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 64



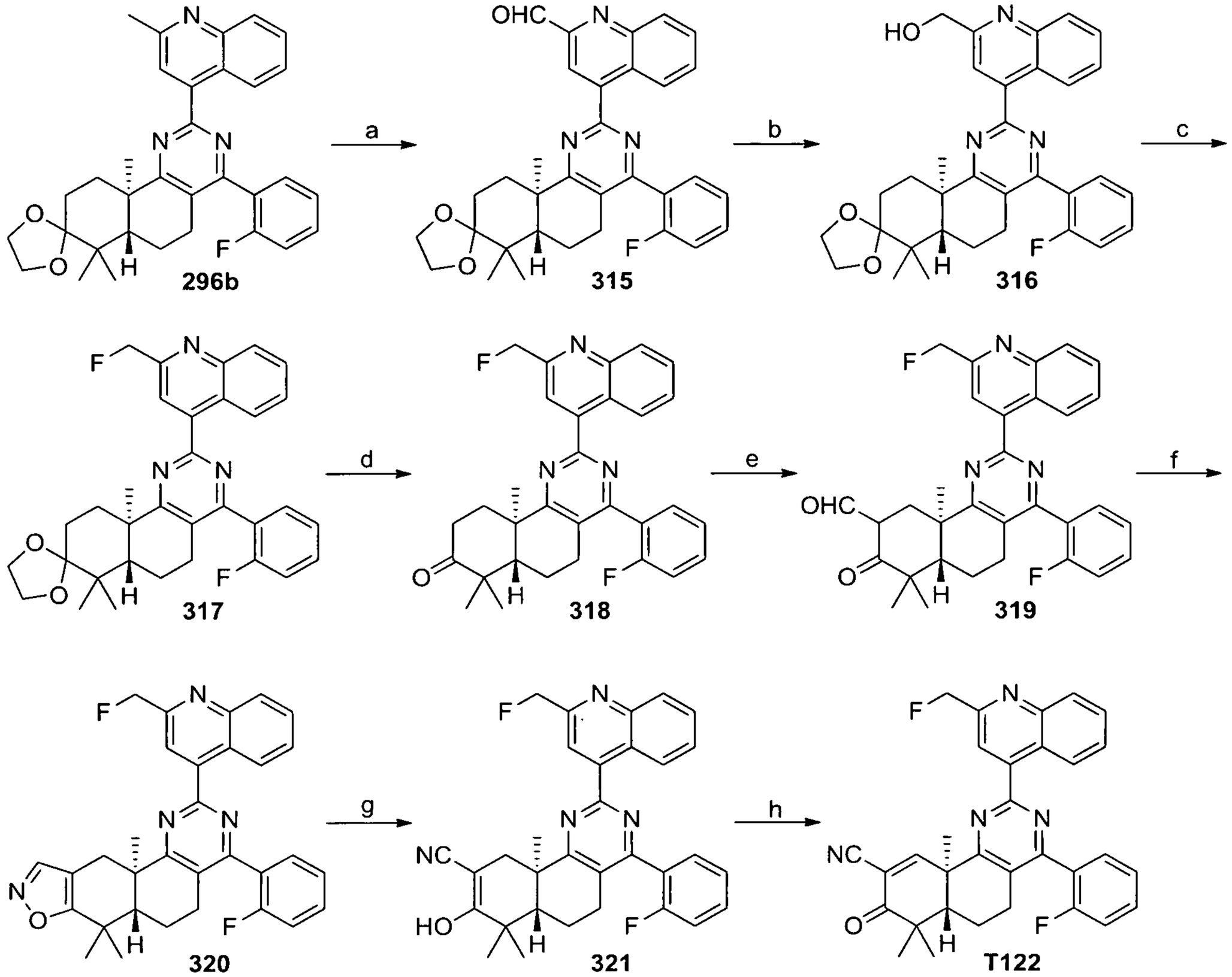
Reagents and conditions: a) SeO_2, 1,4-dioxane, 100 °C; b) $NaBH_4$, EtOH, rt; c) DAST, CH_2Cl_2, 0 °C; d) aq. 3 N HCl, MeOH, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, HOAc, EtOH, 60 °C-rt; g) K_2CO_3, MeOH, rt; h) i) DBDMH, DMF, 0 °C; ii) pyridine, DMF, 60 °C.

Scheme 65



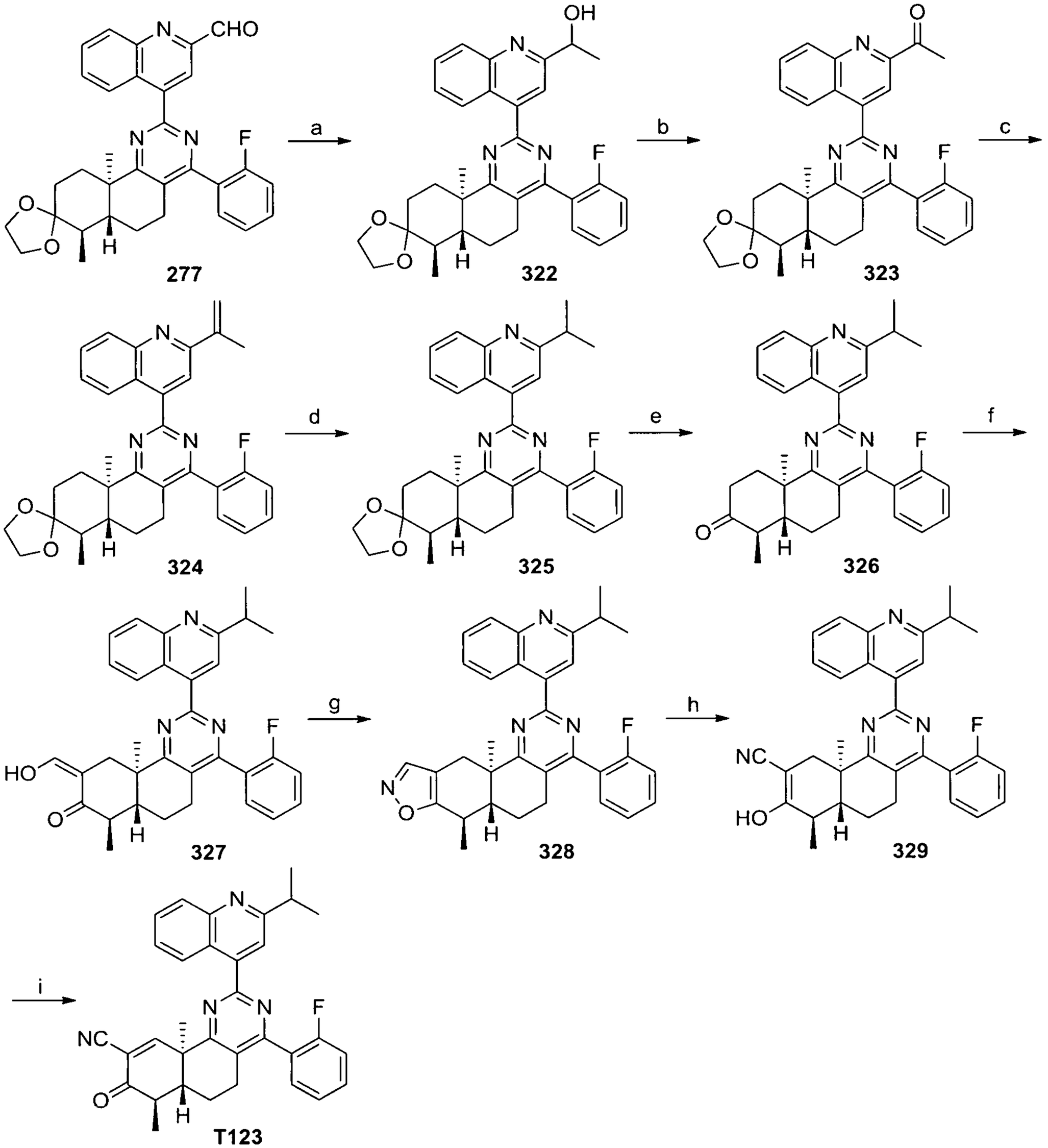
Reagents and conditions: a) 8-fluoro-4-quinolinecarboximidamide hydrochloride, K_2CO_3, EtOH, 40 °C; b) i) $POCl_3$, toluene, microwave, 100 °C; ii) ethylene glycol, $TsOH \cdot H_2O$, benzene, reflux, $-H_2O$; c) NaH, cyclopentanol, THF; d) aq. 3 N HCl, THF, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, AcOH, EtOH, 50 °C; g) K_2CO_3, MeOH, rt; h) i) Br_2, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 66



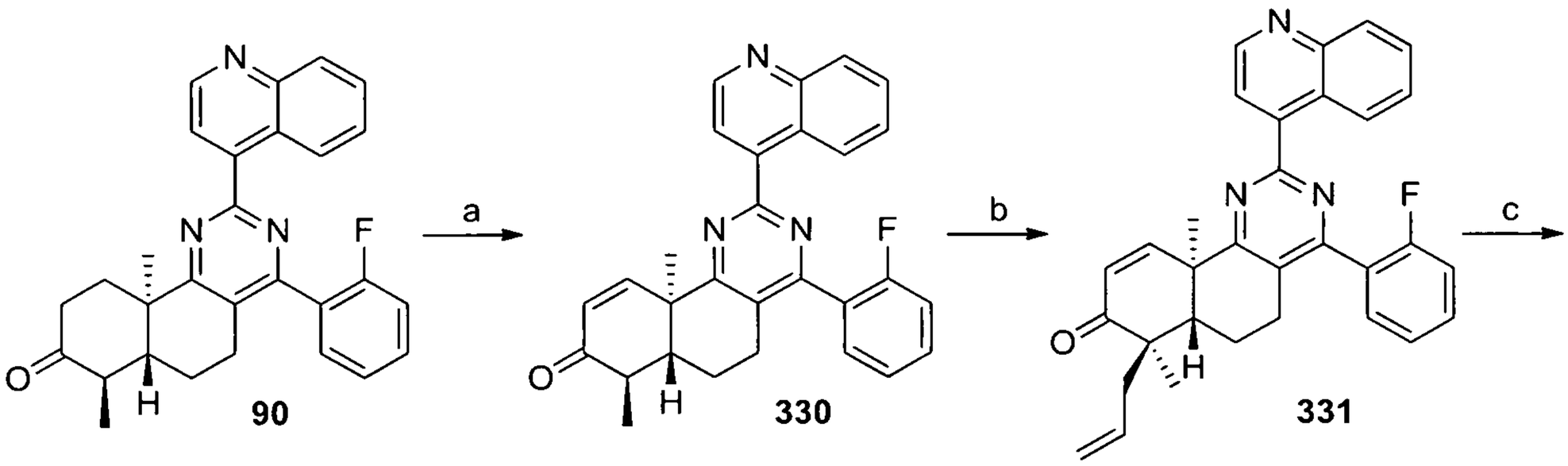
Reagents and conditions: a) SeO_2, 1,4-dioxane, 100 °C; b) $NaBH_4$, EtOH, rt; c) DAST, CH_2Cl_2, 0 °C; d) aq. 3 N HCl, MeOH, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, HOAc, EtOH, 60 °C-rt; g) K_2CO_3, MeOH, rt; h) i) DBDMH, DMF, 0 °C; ii) pyridine, DMF, 60 °C.

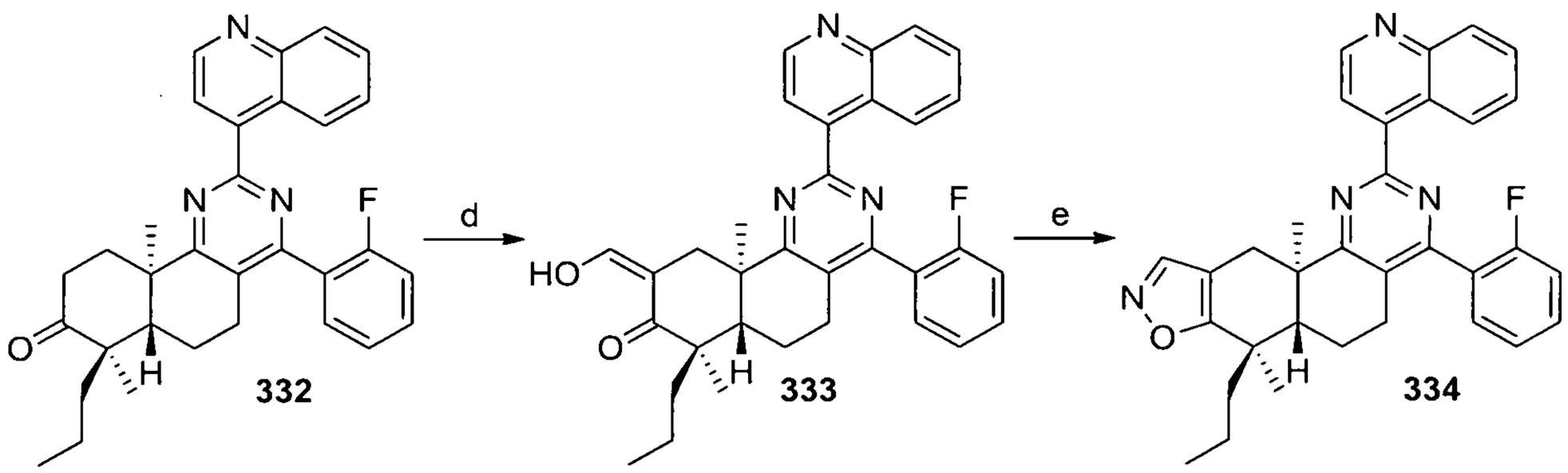
Scheme 67

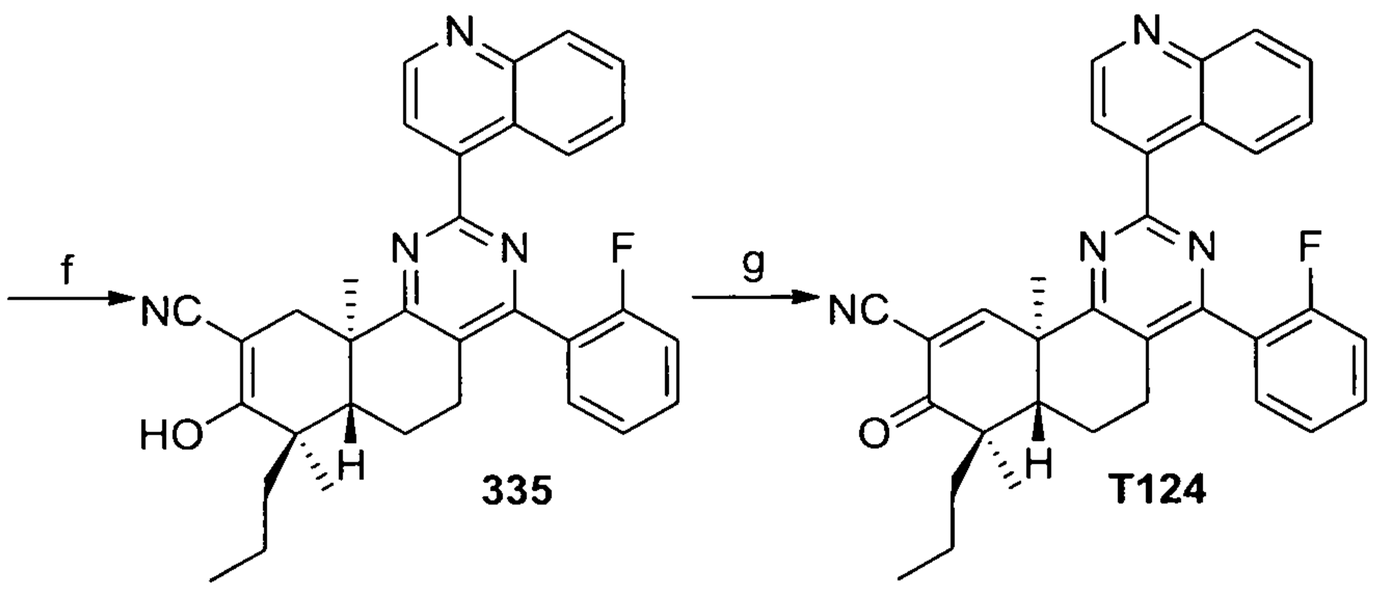


Reagents and conditions: a) MeMgBr, THF, 0 °C-rt; b) MnO_2, CH_2Cl_2, rt; c) $Me(Ph_3P)Br$, *t*-BuOK, THF, 0 °C-rt; d) H_2, Pd/C, MeOH, EtOAc, rt; e) aq. 3 N HCl, THF, rt; f) HCO_2Et, NaOMe, MeOH, 0 °C-rt; g) $NH_2OH{\cdot}HCl$, HOAc, EtOH, 60 °C-rt; h) K_2CO_3, MeOH, rt-50 °C; i) 1) DBDMH, DMF, 0 °C; 2) pyridine, 60 °C.

Scheme 68

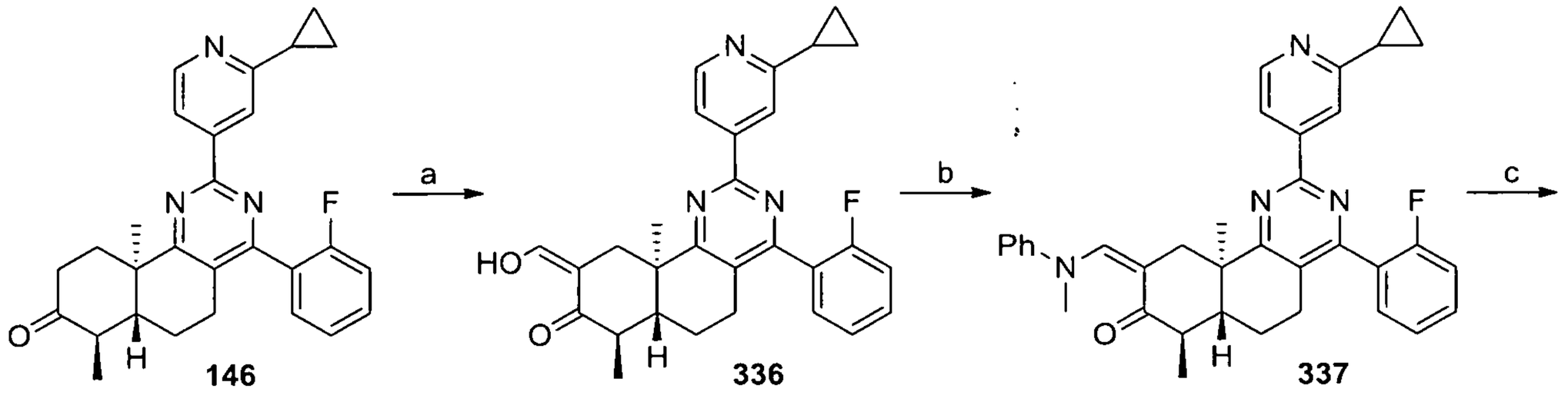






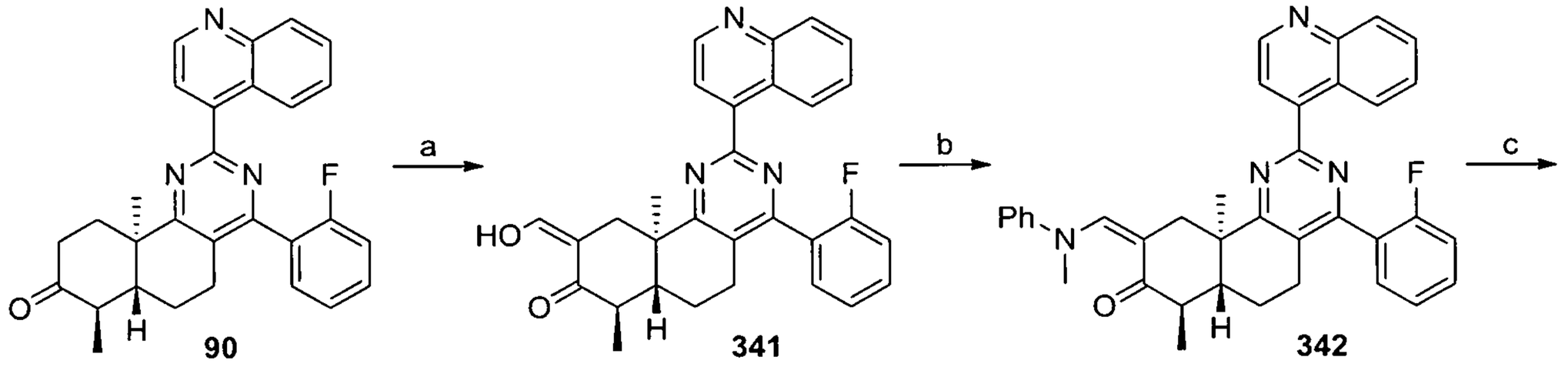
Reagents and conditions: a) IBX, DMSO, 65 °C; b) KH, allyl bromide, THF, 0 °C; c) H_2, 10% Pd/C, MeOH, rt; d) HCO_2Et, NaOMe, MeOH, 0 °C to rt; e) $NH_2OH{\cdot}HCl$, HOAc, EtOH, 60 °C; f) K_2CO_3, MeOH, rt to 50 °C; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 69



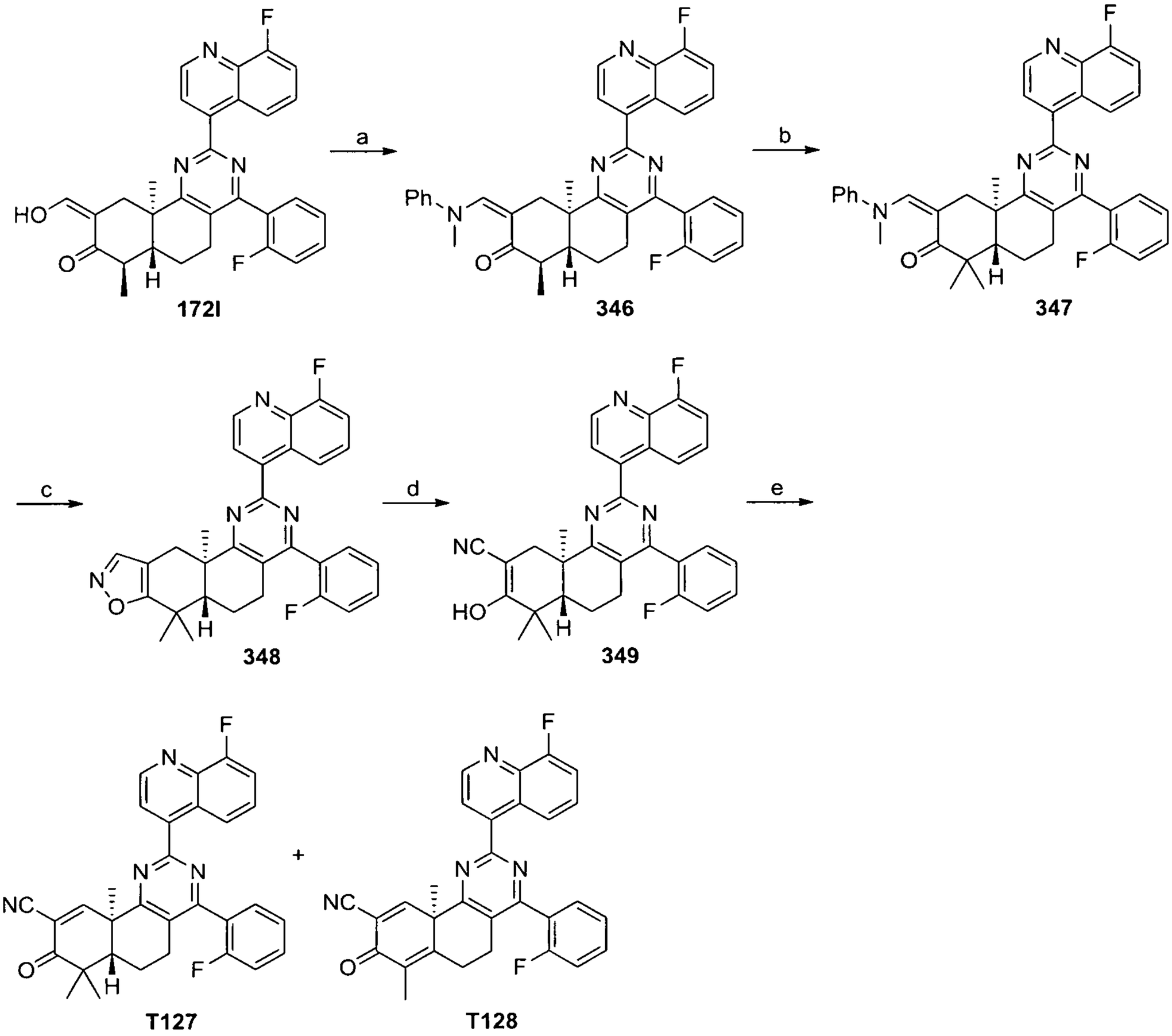
Reagents and conditions: a) HCO_2Et, NaOMe, 0 °C to rt; b) $PhNHCH_3$, $MgSO_4$, *p*-TsOH·H_2O, CH_2Cl_2, rt; c) *t*-BuOK, MeI, THF, 0 °C; d) NH_2OH·HCl, aq. 1 N HCl, EtOH, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 70



Reagents and conditions: a) HCO_2Et, NaOMe, 0 °C to rt; b) $PhNHCH_3$, benzene, reflux,-H_2O, rt; c) *t*-BuOK, EtI, THF, 0 °C; d) $NH_2OH{\cdot}HCl$, aq. 1 N HCl, EtOH, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

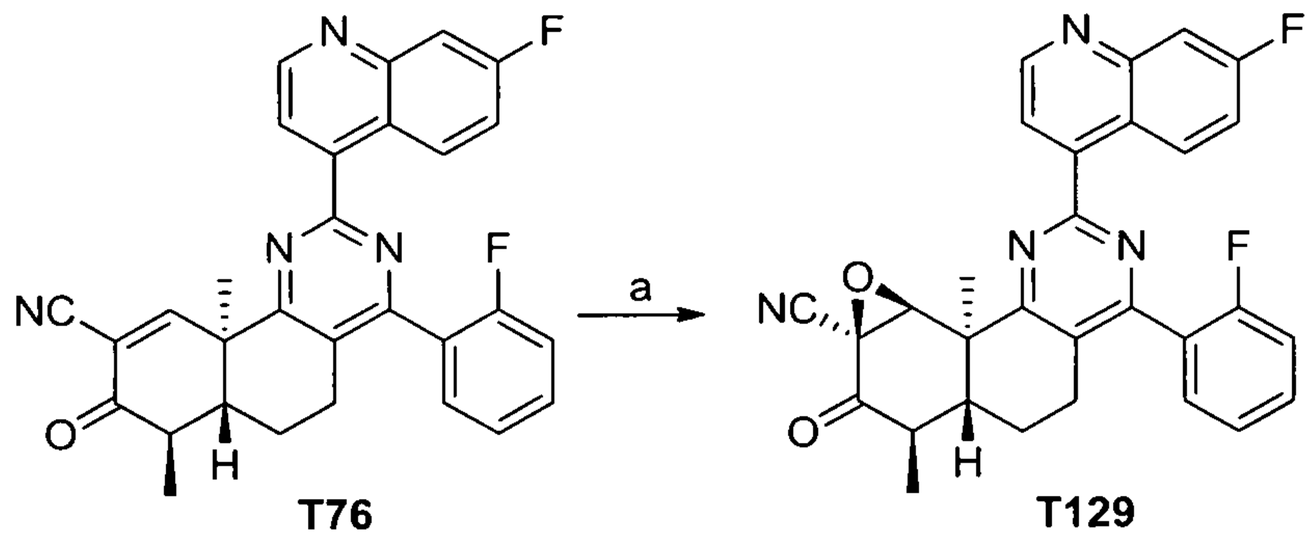
Scheme 71



172I 346 347 348 349 T127 T128

Reagents and conditions: a) *N*-methylaniline, molecular sieve, CH_2Cl_2, rt; b) *t*-BuOK, MeI, THF, 0 °C; c) $NH_2OH \cdot HCl$, EtOH, aq. 1 N HCl, 50 °C; d) K_2CO_3, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

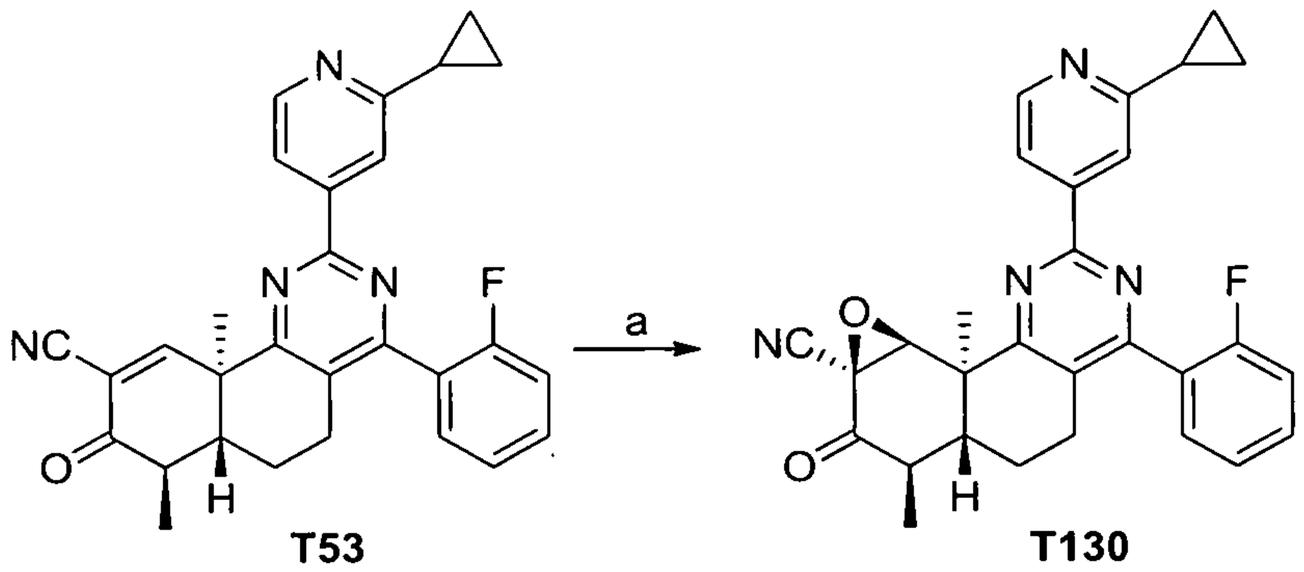
Scheme 72



T76 T129

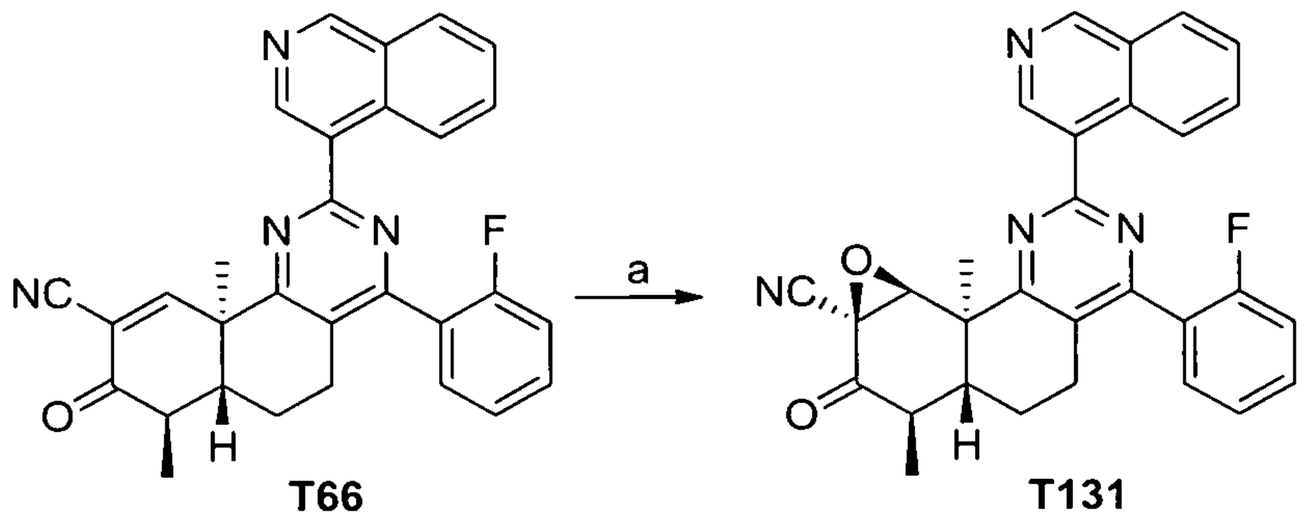
Reagents and conditions: a) aq. 30% H_2O_2, MeCN, rt.

Scheme 73



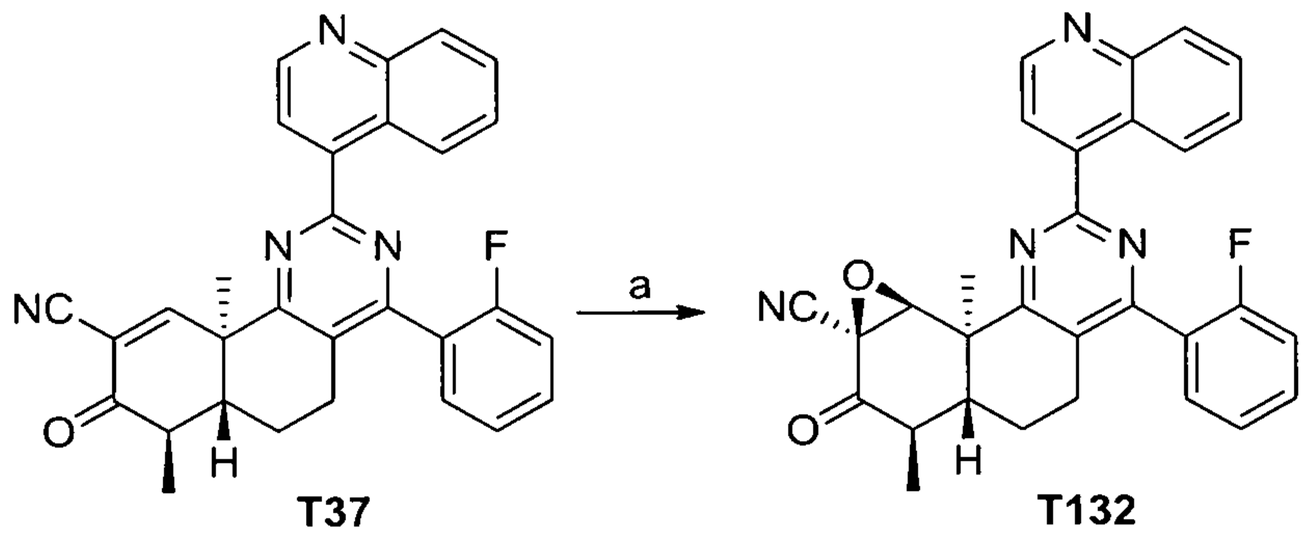
Reagents and conditions: a) aq. 30% H_2O_2, MeCN, rt.

Scheme 74



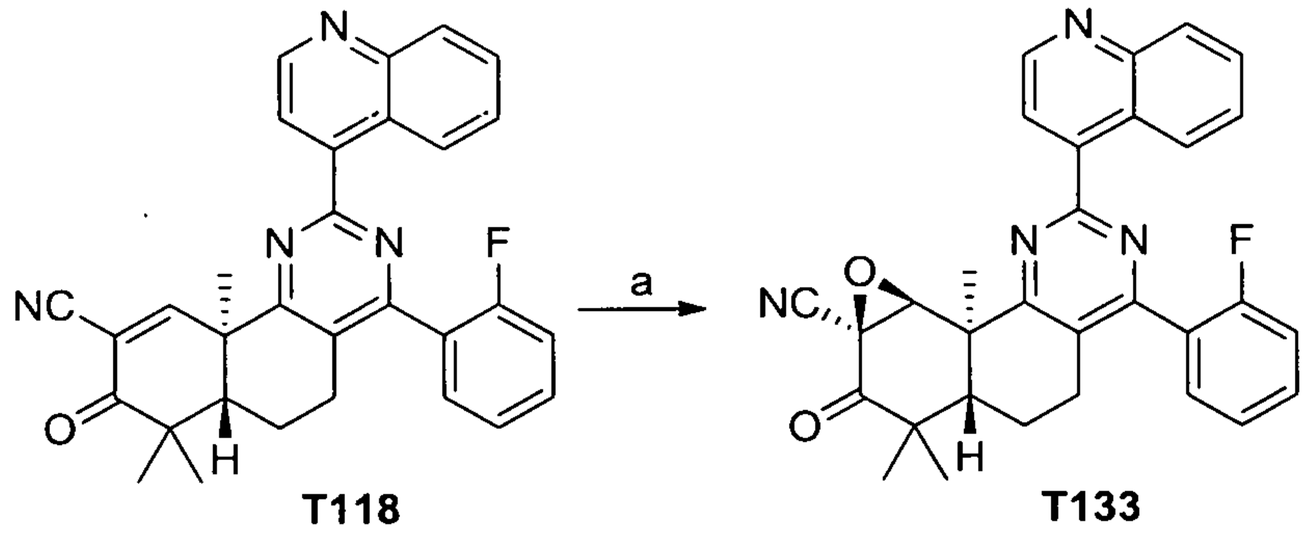
Reagents and conditions: a) aq. 30% H_2O_2, MeCN, rt.

Scheme 75



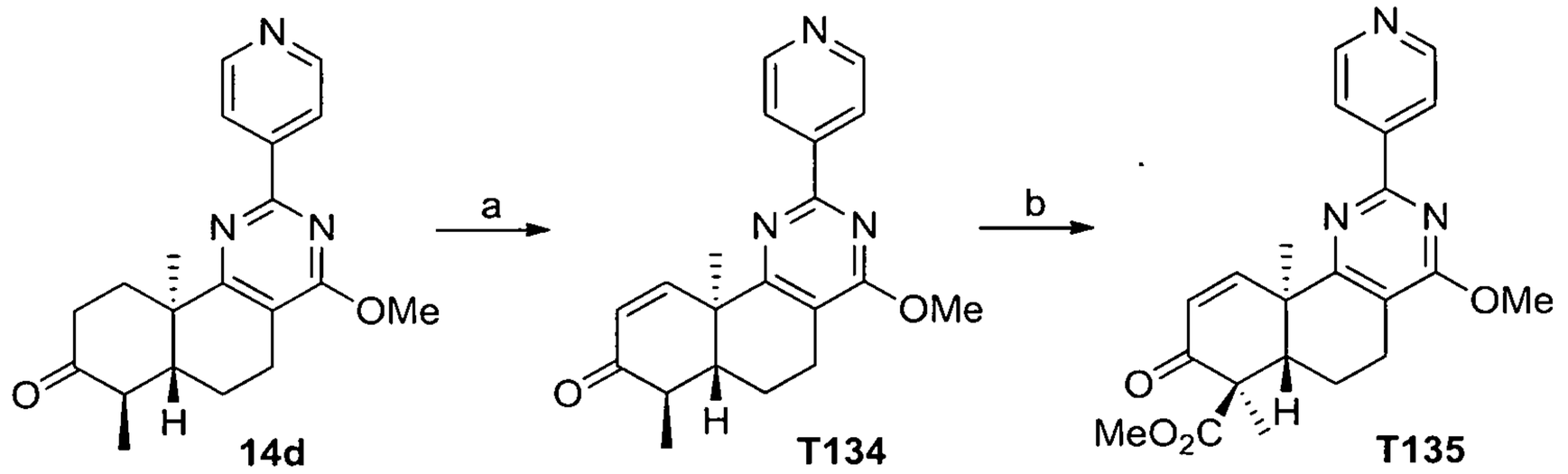
Reagents and conditions: a) aq. 30% H_2O_2, MeCN, rt.

Scheme 76



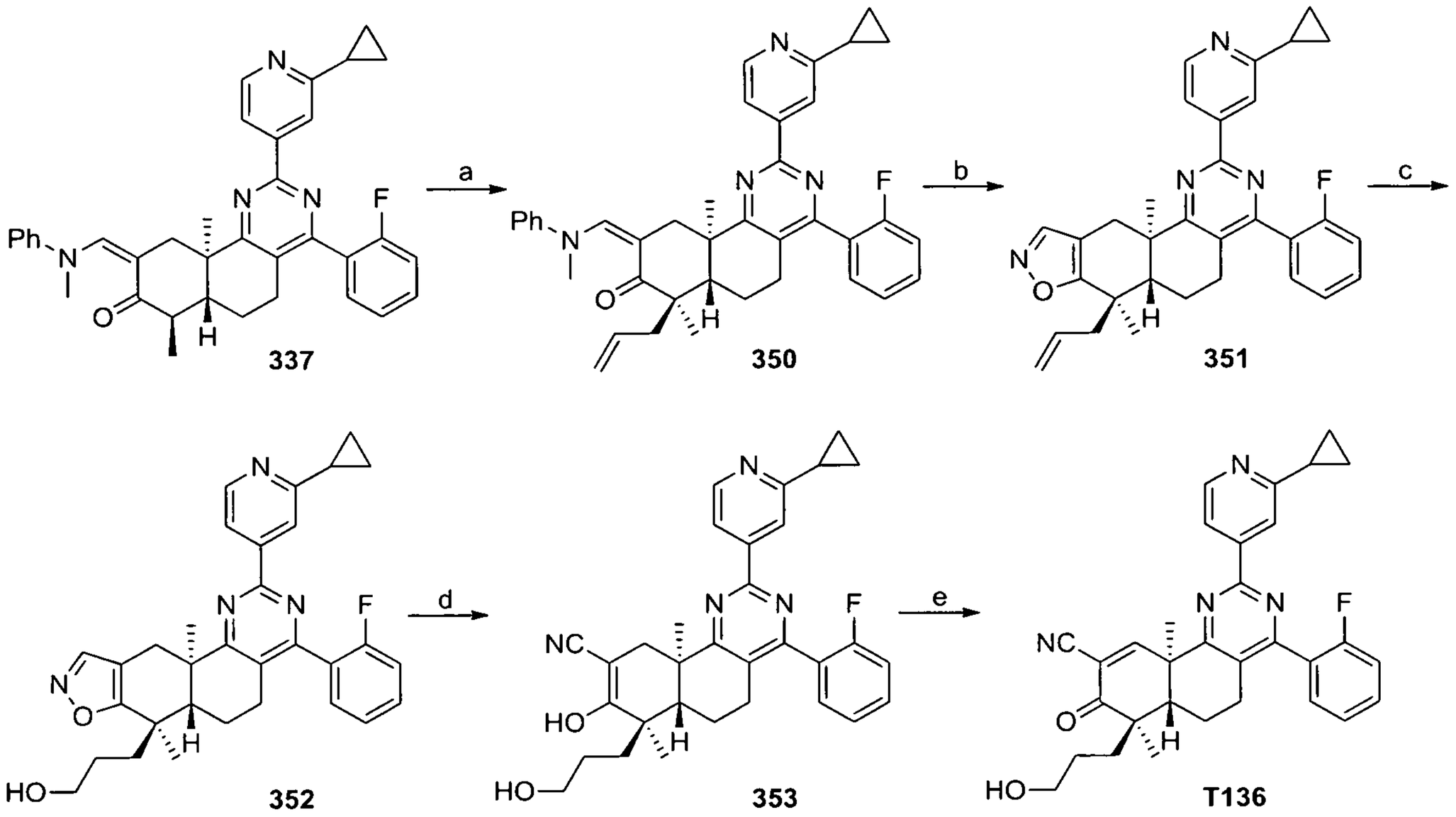
Reagents and conditions: a) aq. 30% H_2O_2, MeCN, rt.

Scheme 77



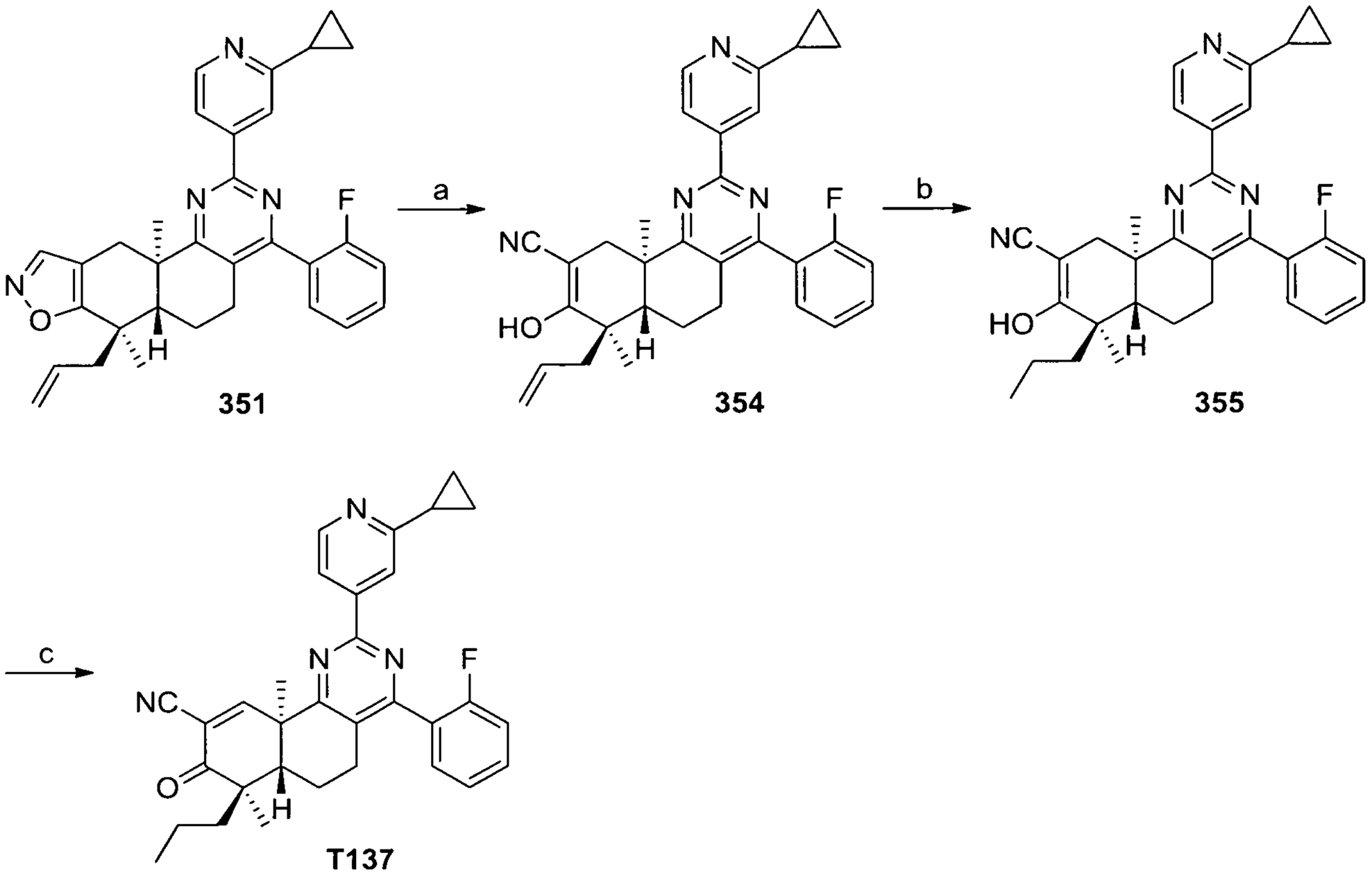
Reagents and conditions: a) i) LHMDS, PhSeCl, THF, -78 °C; ii) 30% aq. H_2O_2, EtOAc, THF, rt; b) LDA, THF, -78 °C to 0 °C; HMPA, $CNCO_2Me$, THF, -78 °C.

Scheme 78



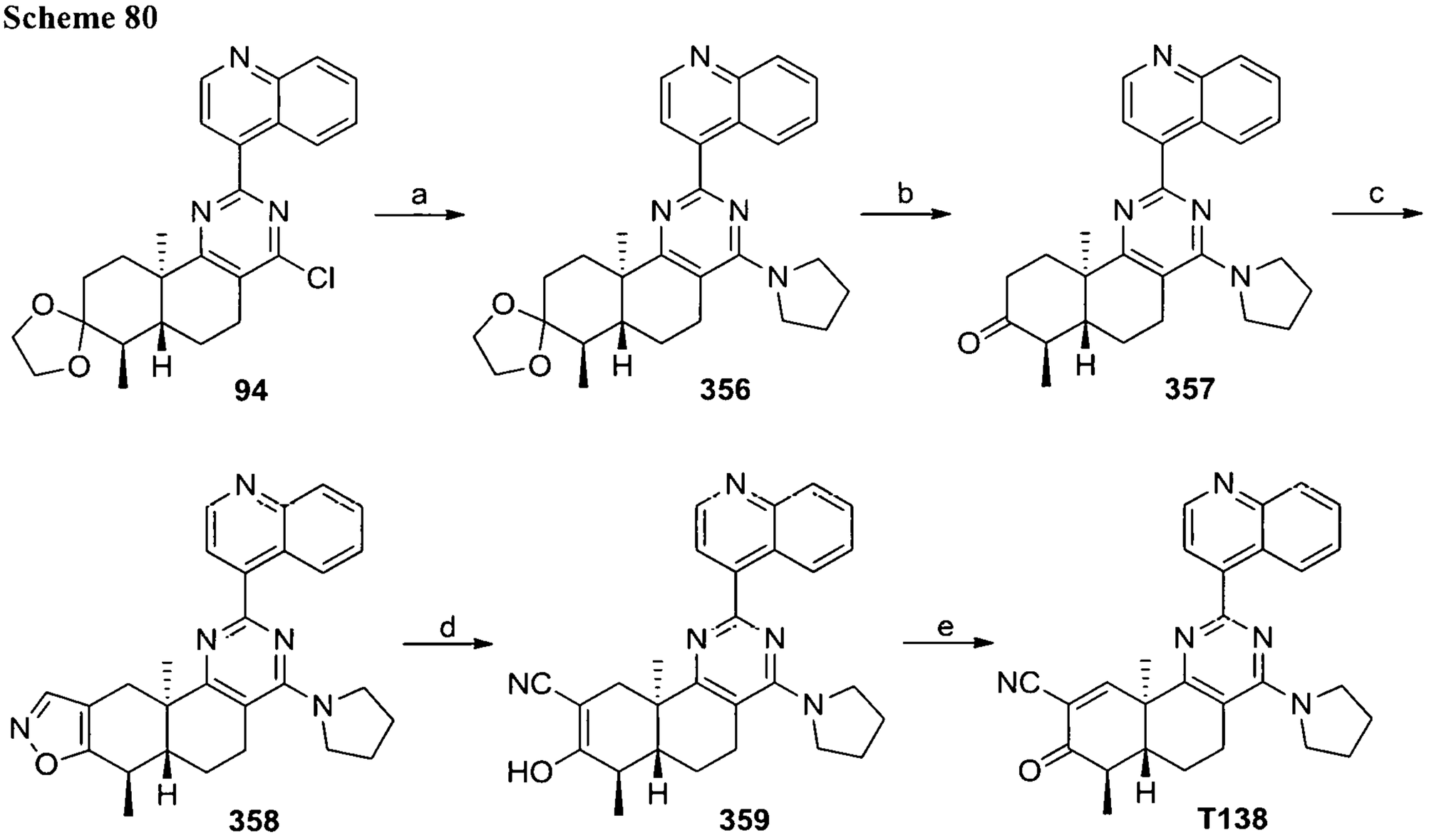
Reagents and conditions: a) *t*-BuOK, allyl bromide, THF, 0 °C; b) $NH_2OH{\cdot}HCl$, aq. 1 N HCl, EtOH, 55 °C; c) i) 9-BBN, THF, rt; ii) H_2O, aq. 3N NaOH, 30% H_2O_2, 0 °C to rt; d) NaOMe, MeOH, 55 °C; e) DDQ, benzene, reflux.

Scheme 79



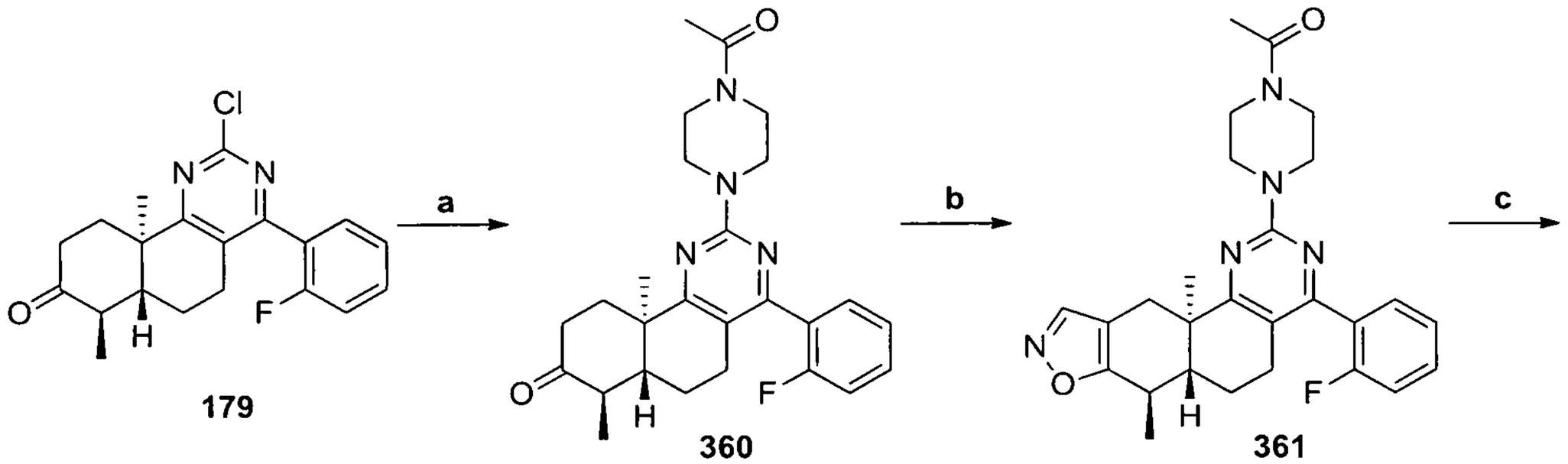
Reagents and conditions: a) K_2CO_3, MeOH, rt; b) 10% Pd/C, H_2, EtOAc, rt; c) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 80



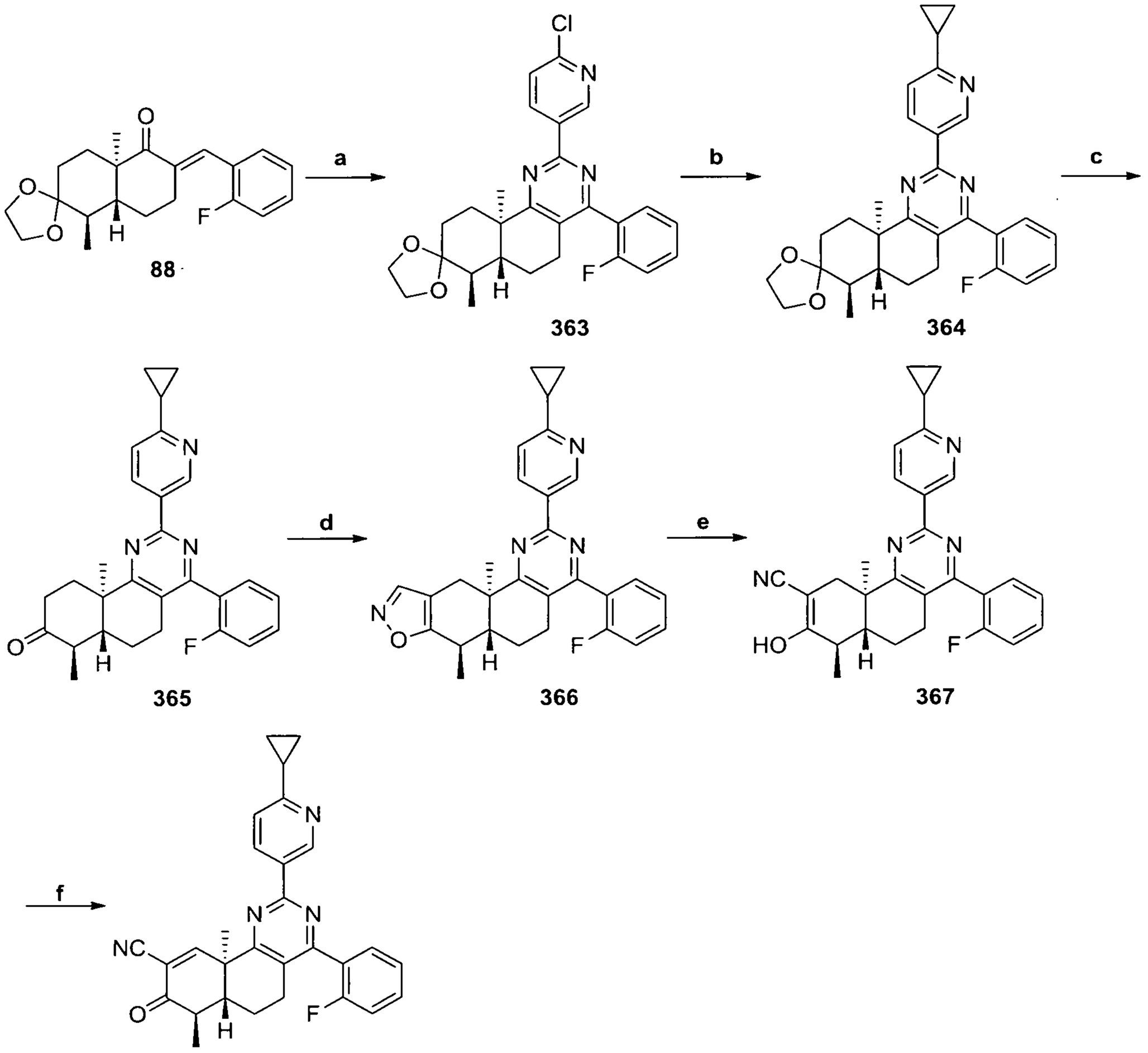
Reagents and conditions: a) pyrrolidine, reflux; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, rt; ii) $NH_2OH \cdot HCl$, aq. 6 N HCl, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 81



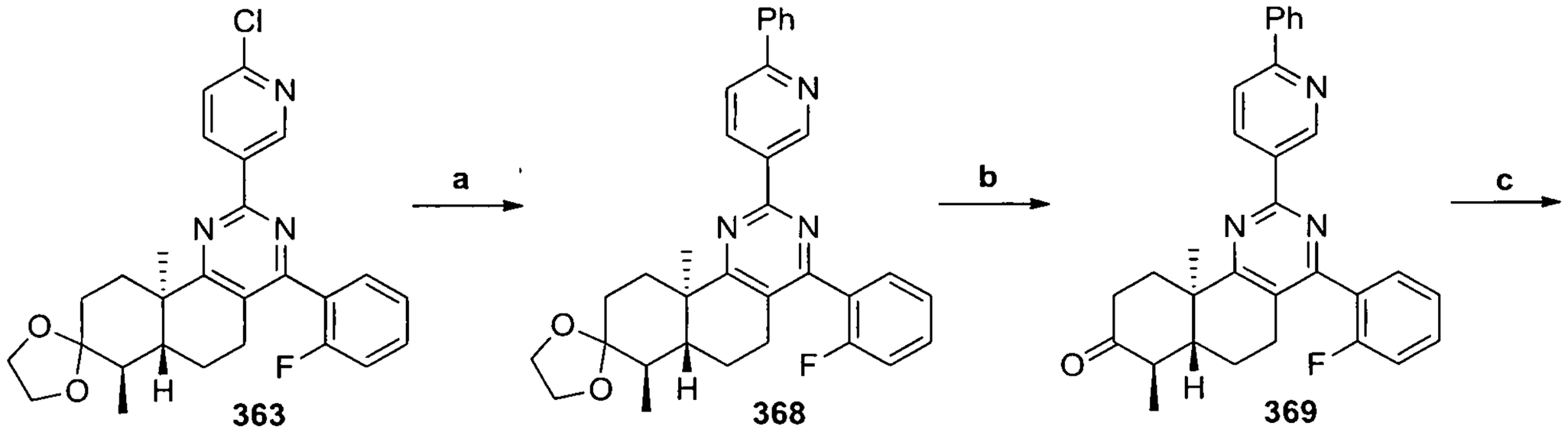
Reagents and conditions: a) 1-acetylpiperazine, NMP, 100 °C; b) i) HCO_2Et, NaOMe, MeOH, THF, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; c) NaOMe, MeOH, 55 °C; d) i) DBDMH, DMF, 0 °C; ii) pyridine, DMF, 55 °C.

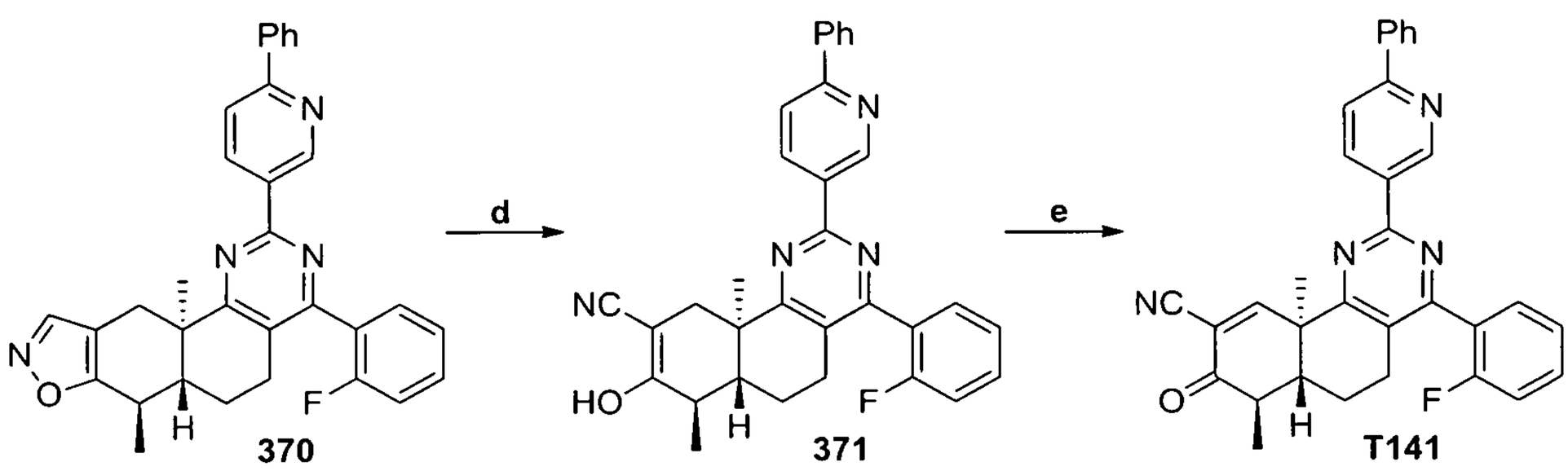
Scheme 82



Reagents and conditions: a) i) 6-chloropyridine-3-carboximidamide hydrochloride, K_2CO_3, EtOH, microwave, 120 °C; ii) DDQ, CH_2Cl_2, rt; b) cyclopropylboronic acid, K_3PO_4, $Pd(OAc)_2$, tricyclohexylphosphine, toluene, H_2O, microwave, 130 °C; c) aq. 3 N HCl, MeOH, rt; d) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

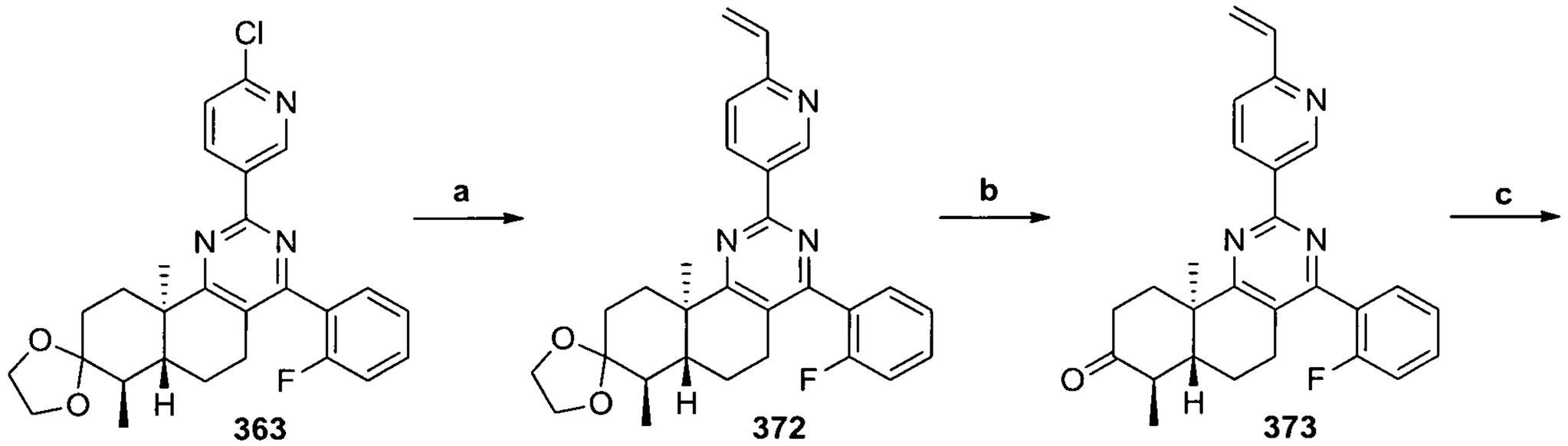
Scheme 83

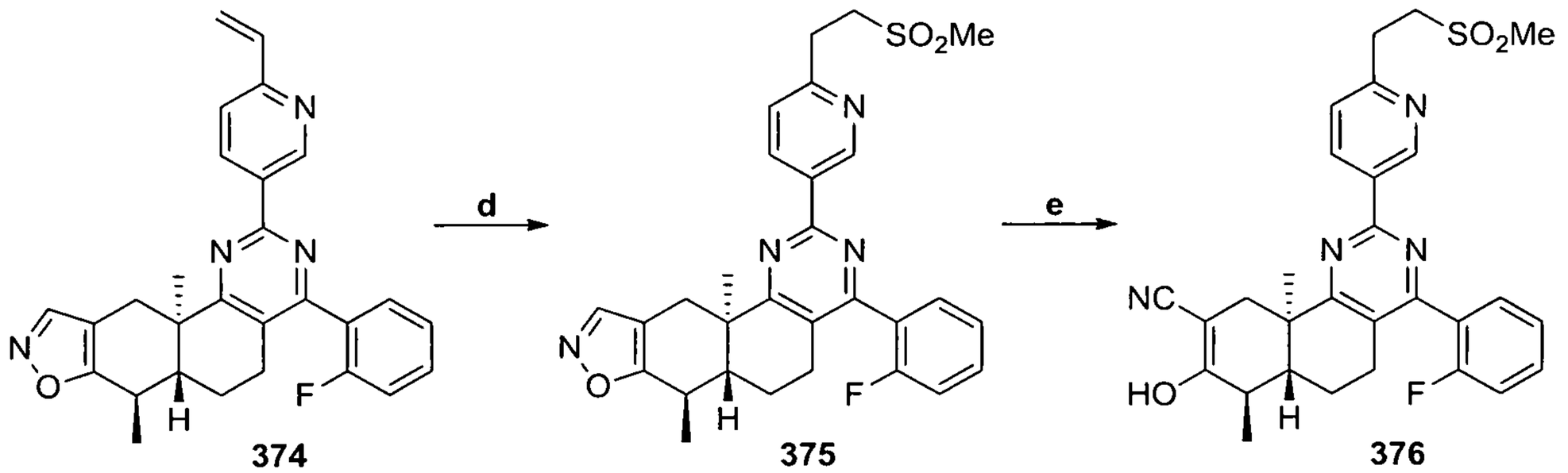


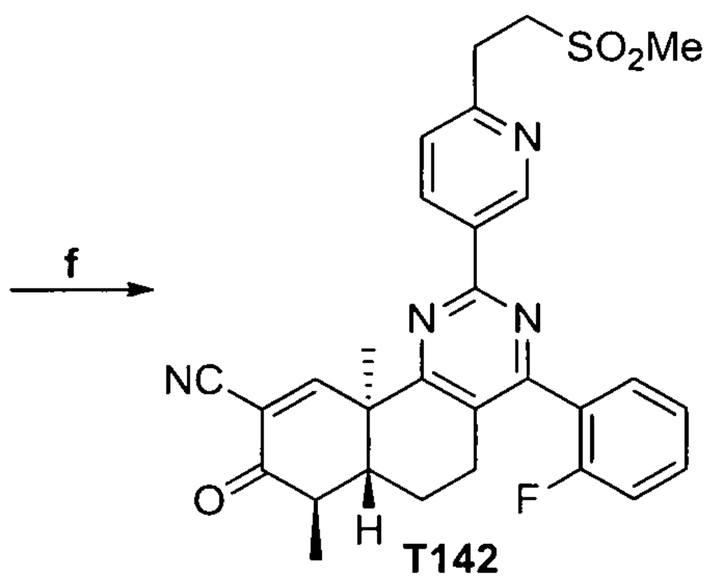


Reagents and conditions: a) $PhB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, toluene, EtOH, H_2O, microwave, 110 °C; b) aq. 3 N HCl, THF, MeOH, rt; c) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH \cdot HCl$, EtOH, 55 °C; d) NaOMe, MeOH, 55 °C; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 84

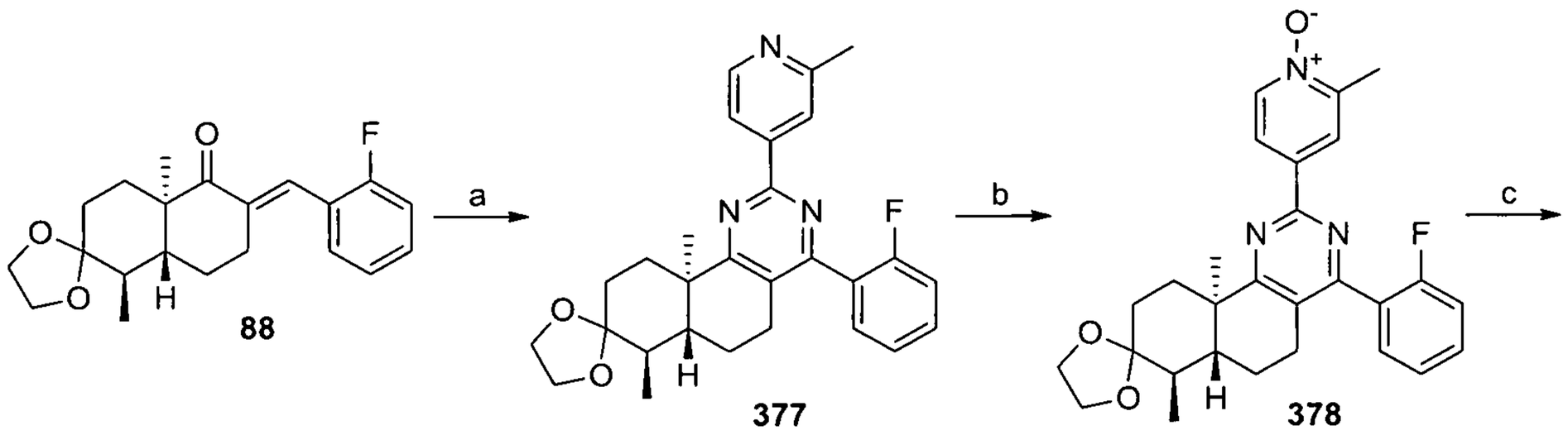






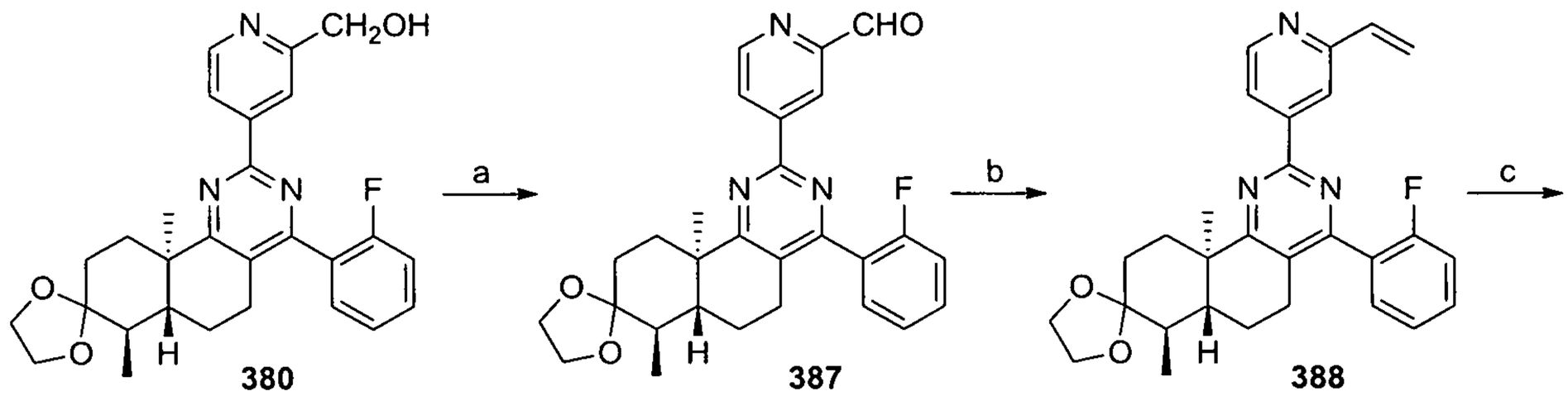
Reagents and conditions: a) potassium vinyltrifluoroborate, K_3PO_4, $Pd_2(dba)_3$, tricyclohexylphosphine, 1,4-dioxane, H_2O, microwave, 140 °C; b) aq. 3 N HCl, MeOH, THF, rt; c) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) $MeSO_2Na$, AcOH, EtOH, 60 °C; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 85



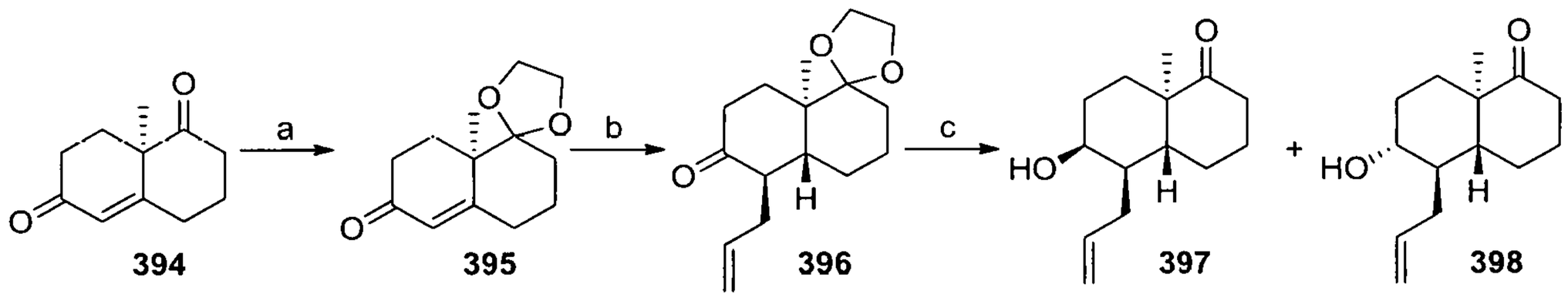
Reagents and conditions: a) 2-methyl-4-pyridinecarboximidamide hydrochloride, K_2CO_3, EtOH, 80 °C; b) *m*-CPBA, CH_2Cl_2, rt; c) Ac_2O, 80 °C; d) K_2CO_3, MeOH, rt; e) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; f) $MeSO_2Na$, DMF, rt; g) aq. 3 N HCl, MeOH, rt; h) HCO_2Et, NaOMe, MeOH, 0 °C to rt; i) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C; j) K_2CO_3, MeOH, rt; k) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 86



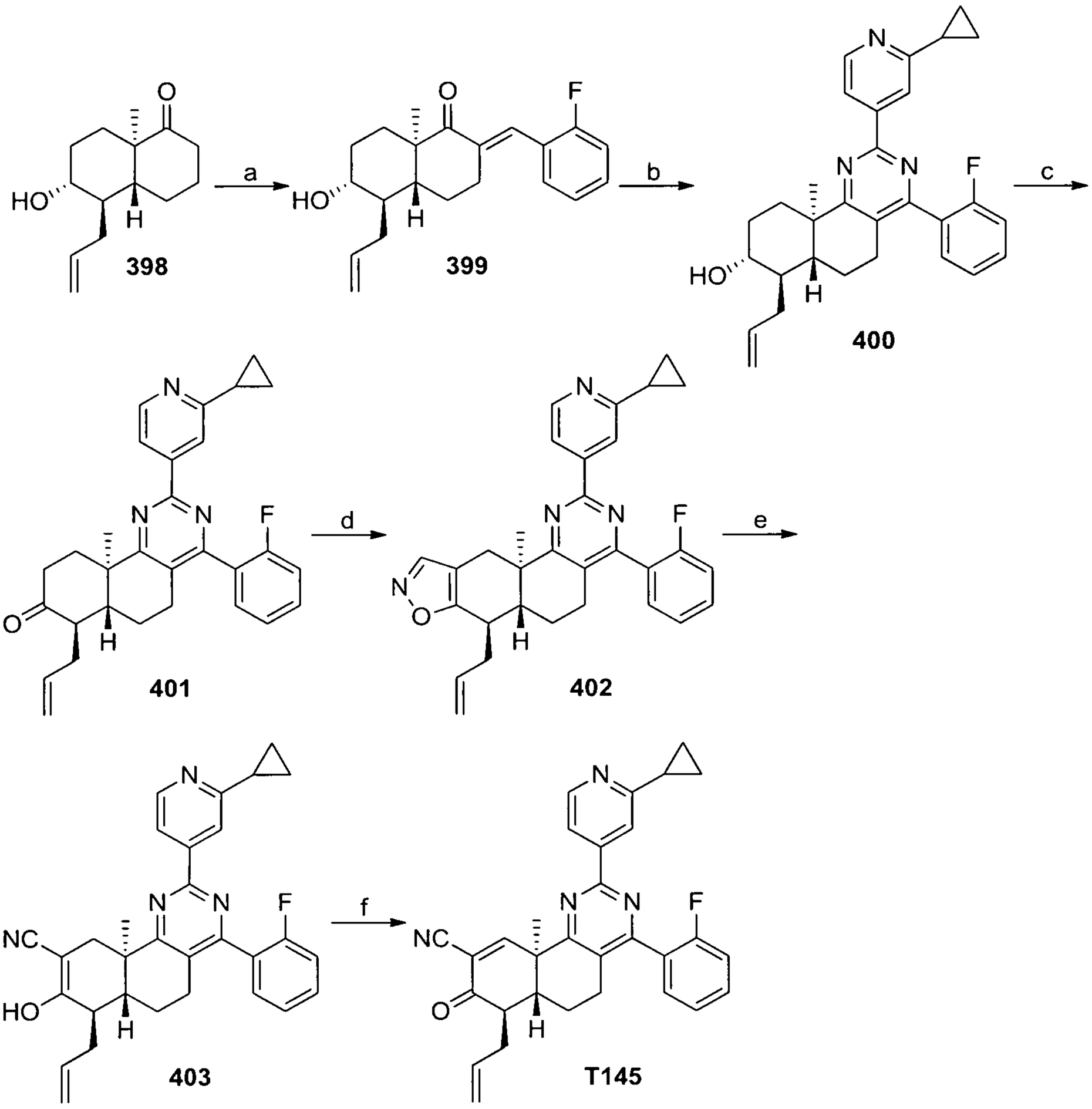
Reagents and conditions: a) MnO_2, CH_2Cl_2, rt; b) $MePPh_3Br$, *t*-BuOK, THF, 0 °C-rt; c) aq. 3 N HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, 0 °C to rt; e) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C; f) $MeSO_2Na$, AcOH, EtOH, 60 °C; g) K_2CO_3, MeOH, rt; h) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 87



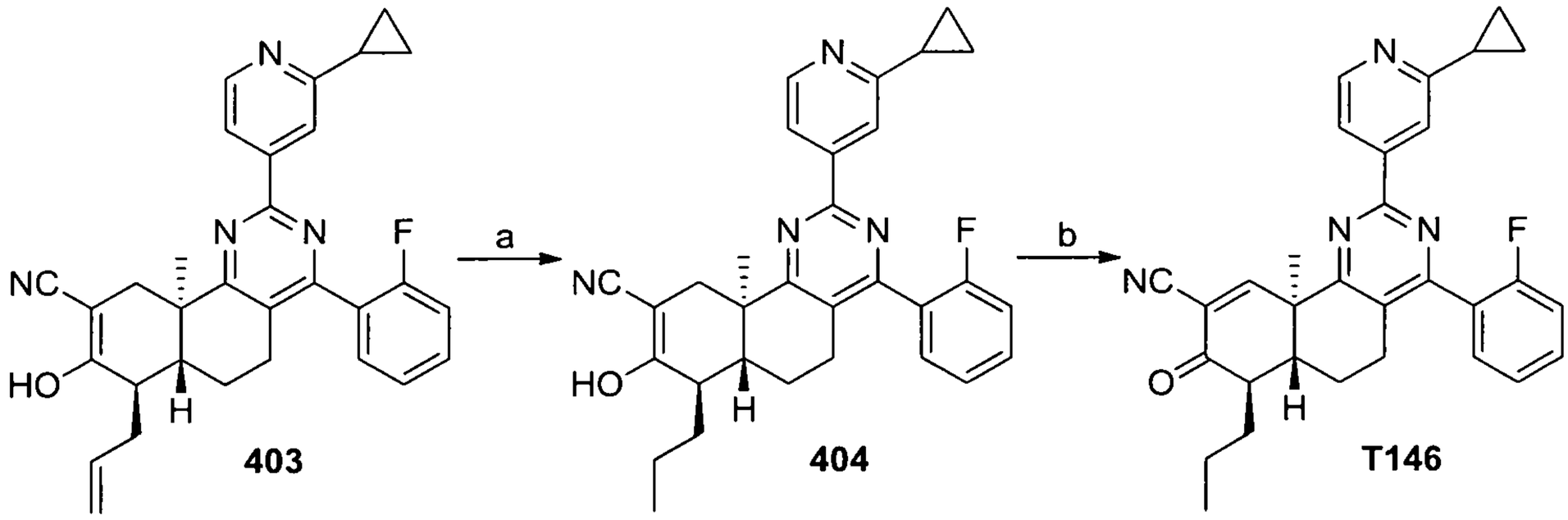
Reagents and conditions: a) ethylene glycol, *p*-TsOH·H_2O, rt; b) Li/NH_3 (l), THF, H_2O, −78 °C; allyl bromide, −78 °C; c) i) $NaBH_4$, EtOH, 0 °C; ii) aq. 3 N HCl, rt.

Scheme 88



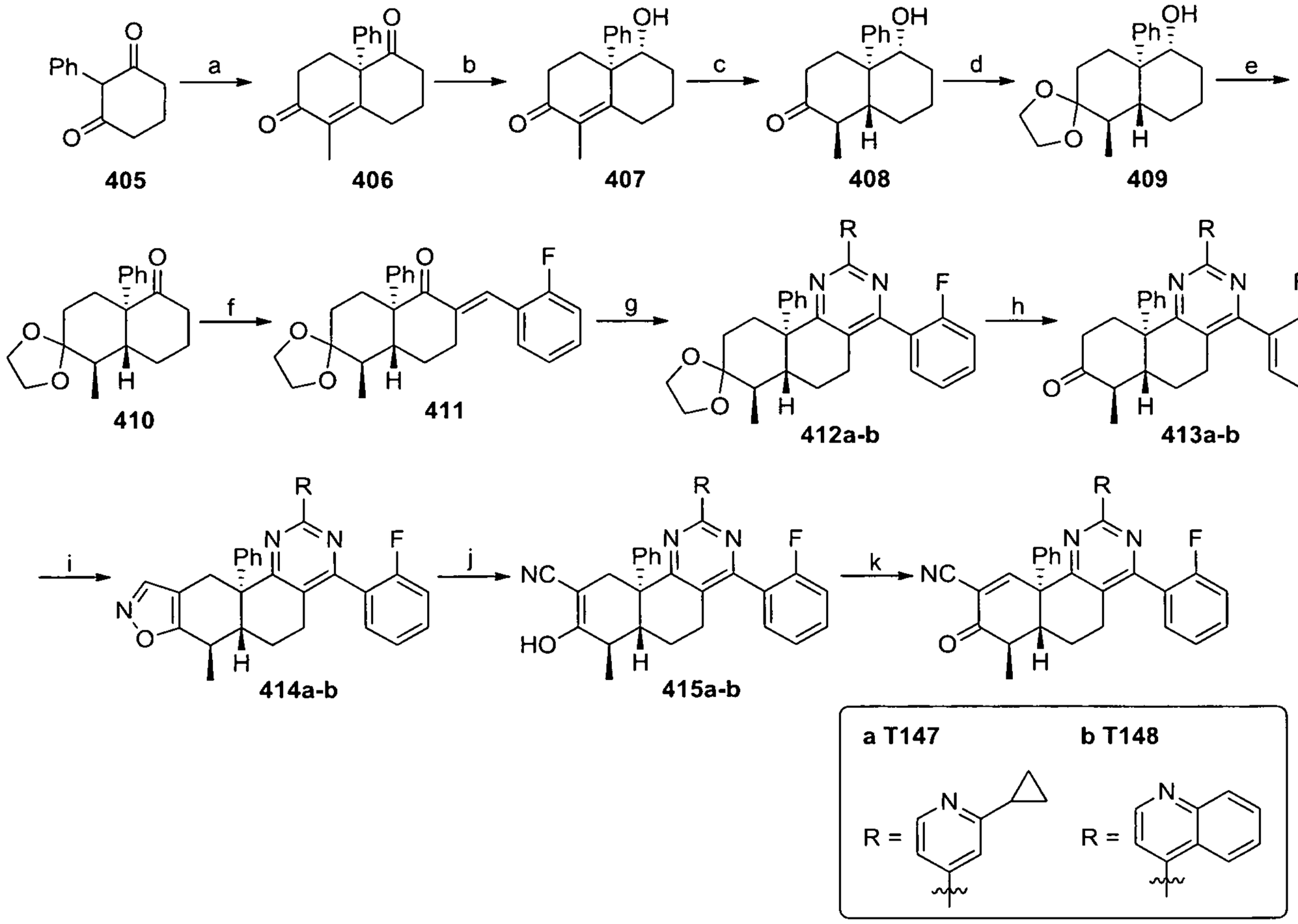
Reagents and conditions: a) 2-fluorobenzaldehyde, KF/Al_2O_3, EtOH, rt; b) i) 2-cyclopropyl-4-carboximidamide pyridine hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; c) Dess-Martin periodinane, CH_2Cl_2, rt; d) i) HCO_2Et, NaOMe, MeOH, 0 °C-rt; ii) $NH_2OH{\cdot}HCl$, EtOH, H_2O, 55 °C; e) NaOMe, MeOH, 55 °C; f) DDQ, toluene, 85 °C.

Scheme 89



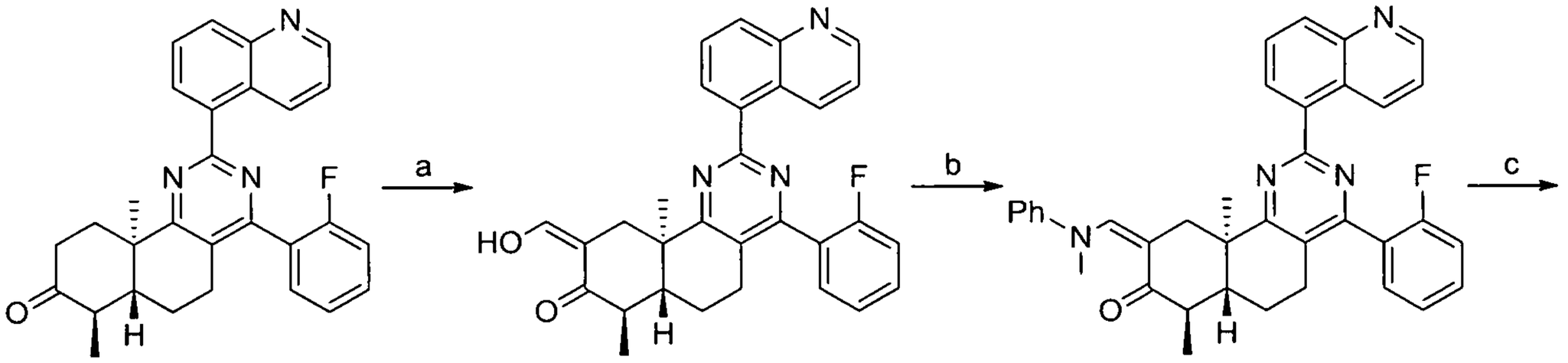
Reagents and conditions: a) H_2, 10% Pd/C, EtOAc, rt; b) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 90

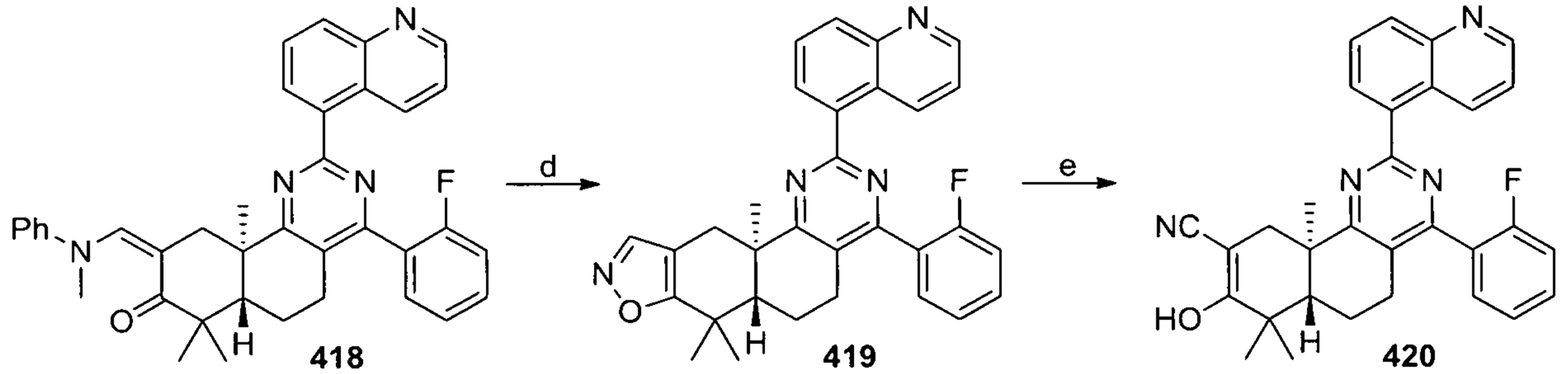


Reagents and conditions: a) i) Ethyl vinyl ketone, Et_3N, MeCN, 75 °C; ii) D-phenylalanine, PPTS, DMSO, 45 °C; b) i) $NaBH_4$, EtOH, 0 °C; ii) crystallization; c) i) H_2, 10% Pd/C, pyridine, THF, rt; ii) aq. 3 N HCl, EtOH, rt; d) ethylene glycol, *p*-TsOH·H_2O, toluene, reflux, -H_2O; e) $Na_2WO_4 \cdot 2H_2O$, $Na_2HPO_4 \cdot 12H_2O$, aq. 30% H_2O_2, DMA, 90 °C; f) 2-fluorobenzaldehyde, KF/Al_2O_3, EtOH, THF, rt; g) i) amidine hydrochloride, K_2CO_3, EtOH, reflux; ii) DDQ, CH_2Cl_2, rt; h) aq. 3 N HCl, MeOH, THF, rt; i) 1) HCO_2Et, NaOMe, MeOH, 0 °C-rt; 2) aq. 6 N HCl, $NH_2OH \cdot HCl$, EtOH, H_2O, 55 °C; j) NaOMe, MeOH, 55 °C; k) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 91



188c 416 417

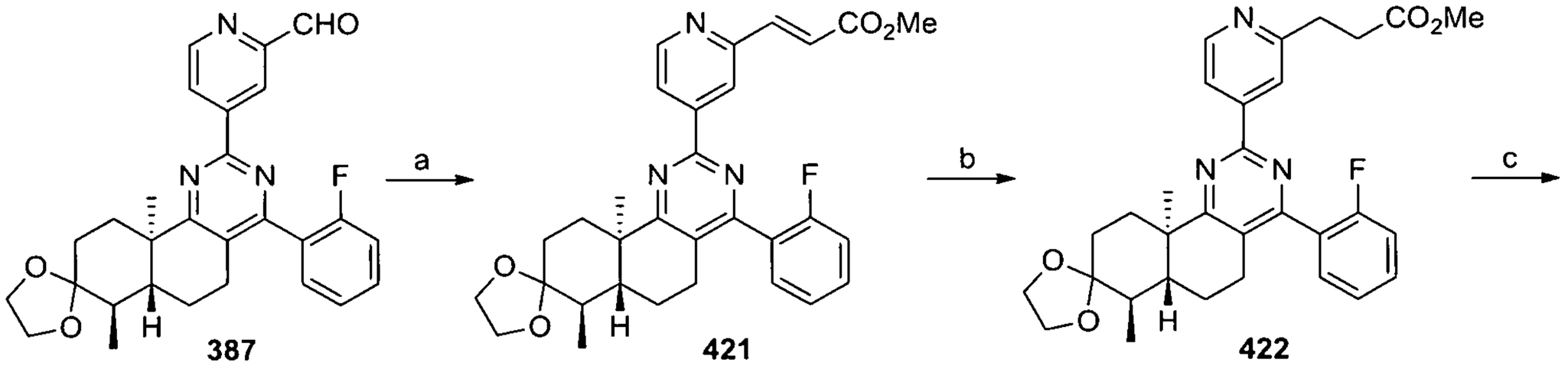


418 419 420

T149

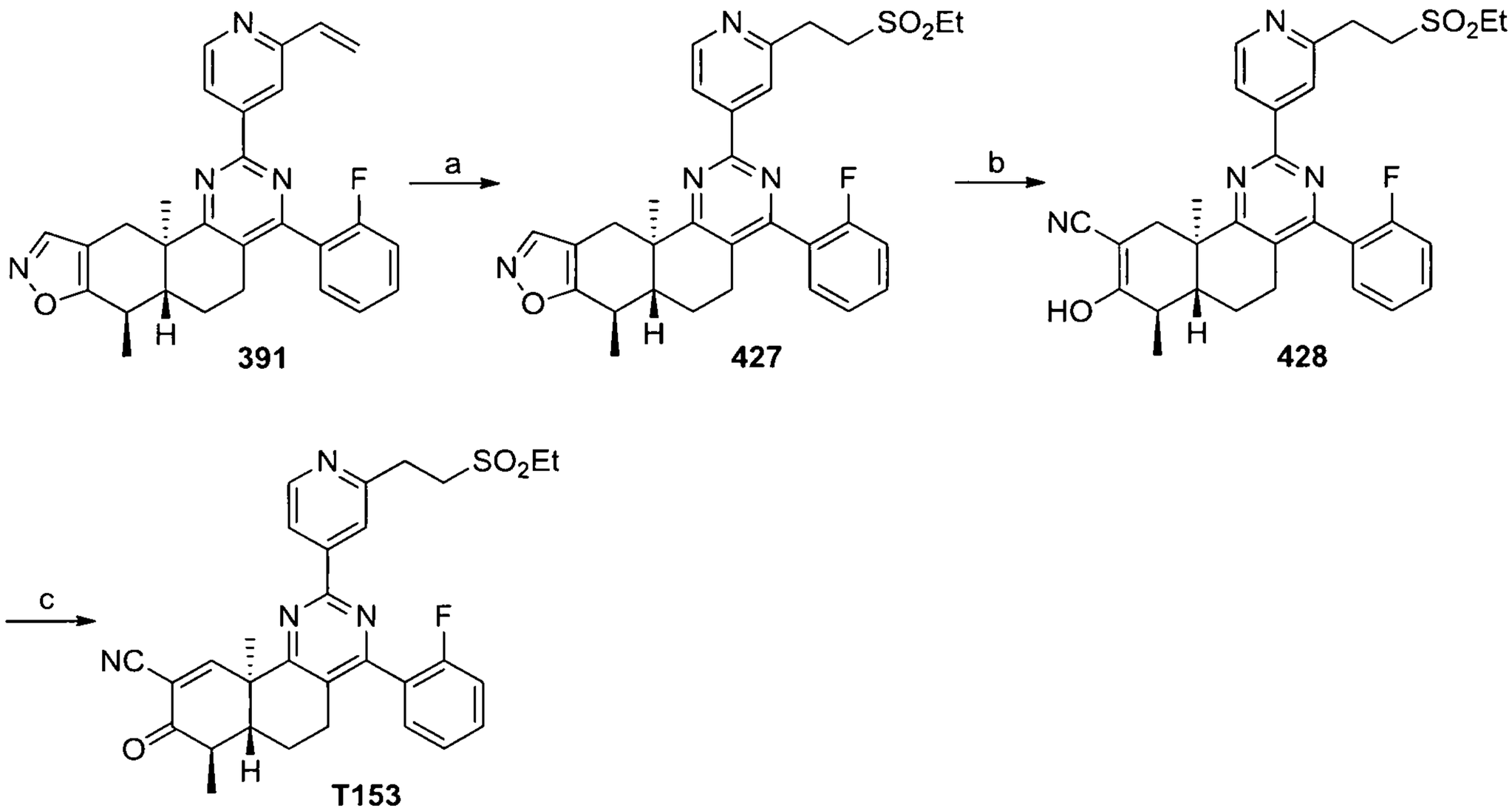
Reagents and conditions: a) HCO_2Et, NaOMe, MeOH, rt; b) *N*-methylaniline, *p*-TsOH·H_2O, $MgSO_4$, CH_2Cl_2, rt; c) *t*-BuOK, MeI, THF, 0 °C; d) NH_2OH·HCl, aq. 1 N HCl, EtOH, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 92



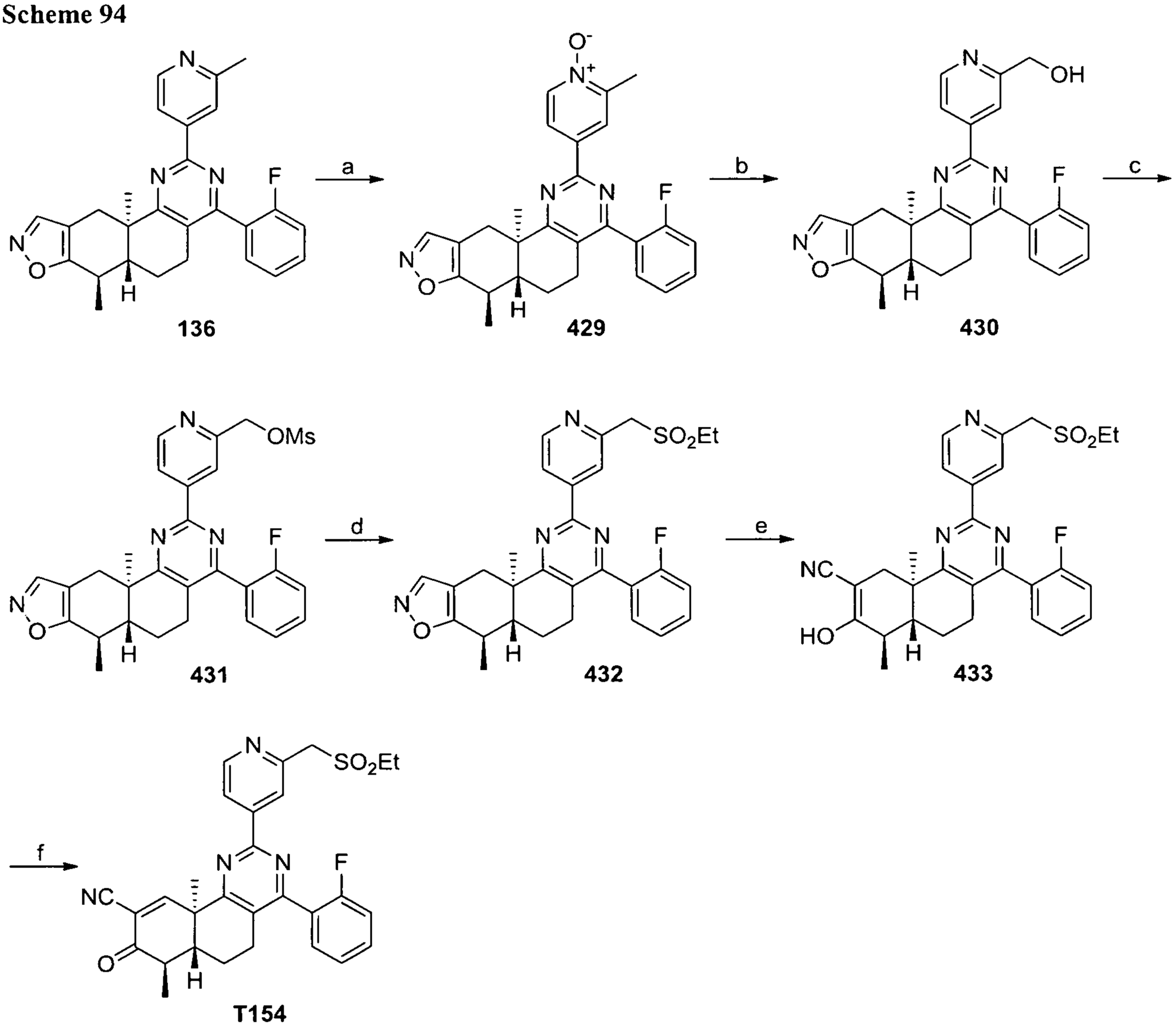
Reagents and conditions: a) methyl (triphenylphosphoranylidene)acetate, benzene, 80 °C; b) H_2, 10% Pd/C, EtOAc, rt; c) aq. 3 N HCl, MeOH, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH{\cdot}HCl$, AcOH, EtOH, 60 °C; f) K_2CO_3, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C; h) aq. 1 N HCl, EtOH, 50 °C; i) $Me_2NH{\cdot}HCl$, HATU, DIPEA, CH_2Cl_2, 0 °C to rt.

Scheme 93



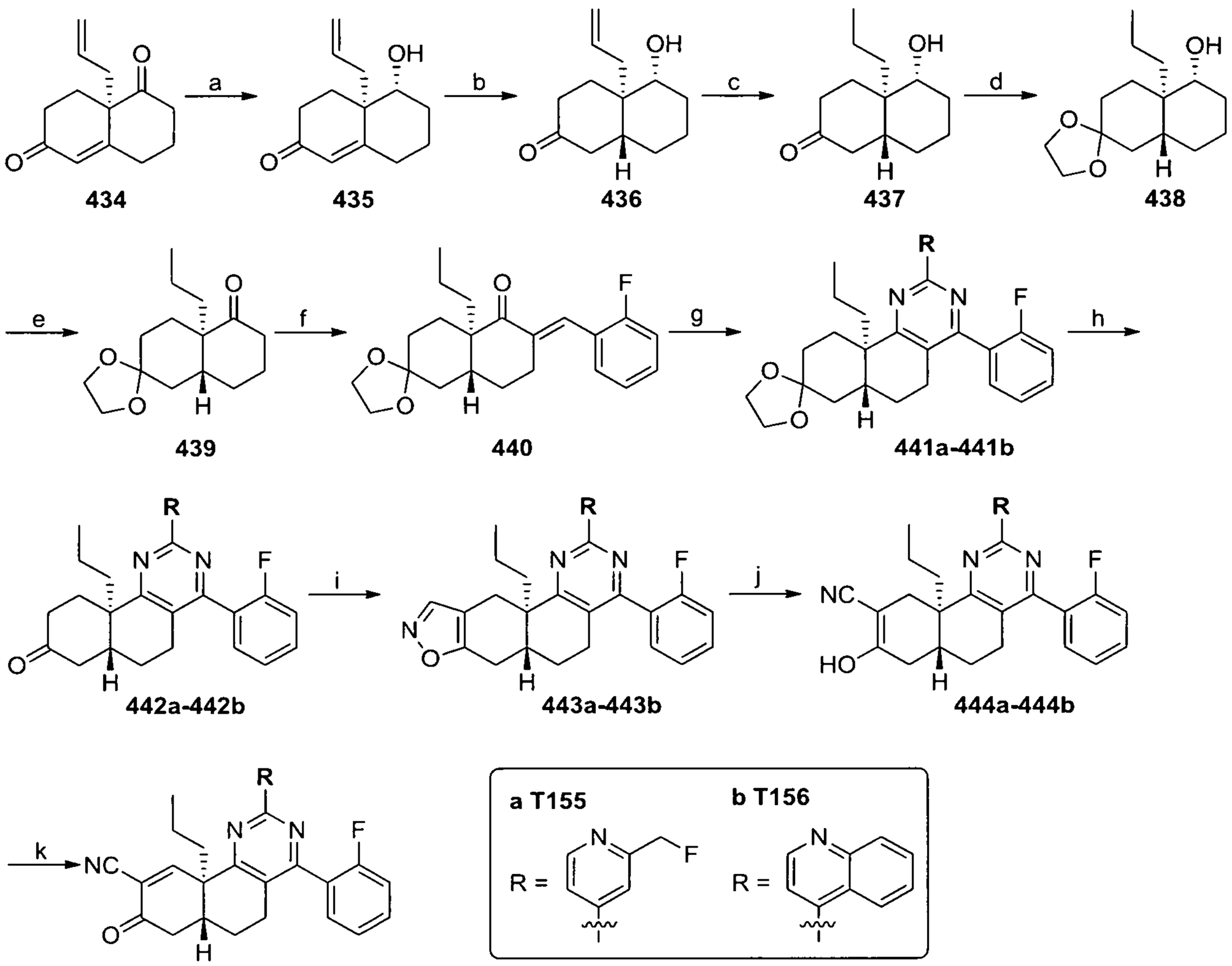
Reagents and conditions: a) $EtSO_2Na$, AcOH, EtOH, 60 °C; b) K_2CO_3, MeOH, rt; c) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 94



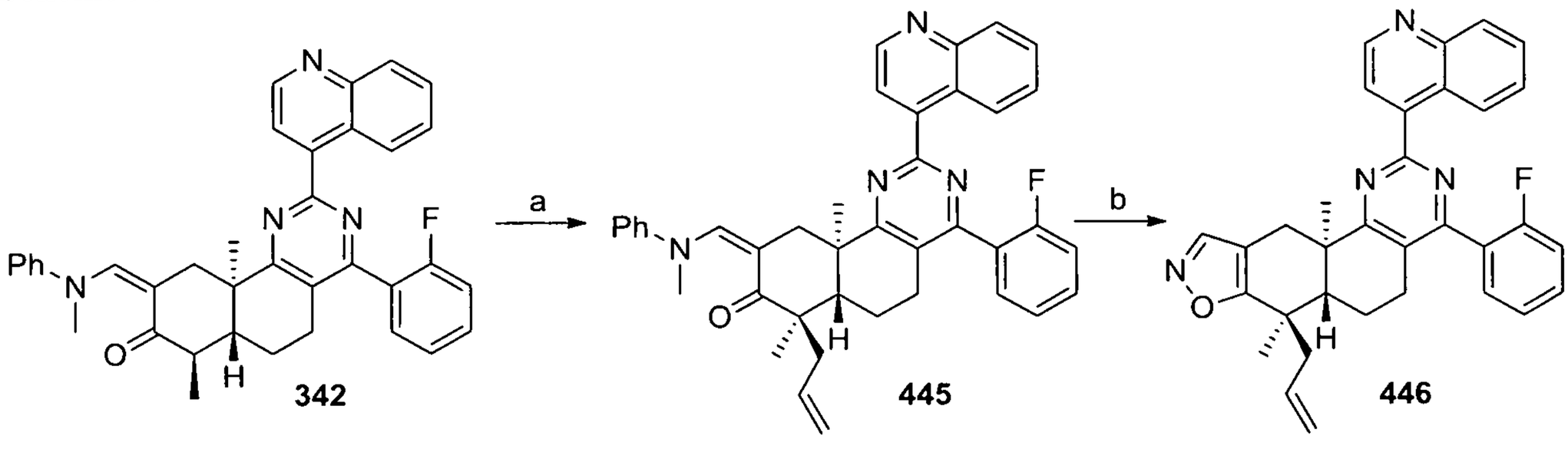
Reagents and conditions: a) *m*-CPBA, CH_2Cl_2, rt; b) i) TFAA, CH_2Cl_2, rt; ii) sat. aq. $NaHCO_3$, EtOAc, rt; c) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; d) $EtSO_2Na$, DMF, rt; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 95



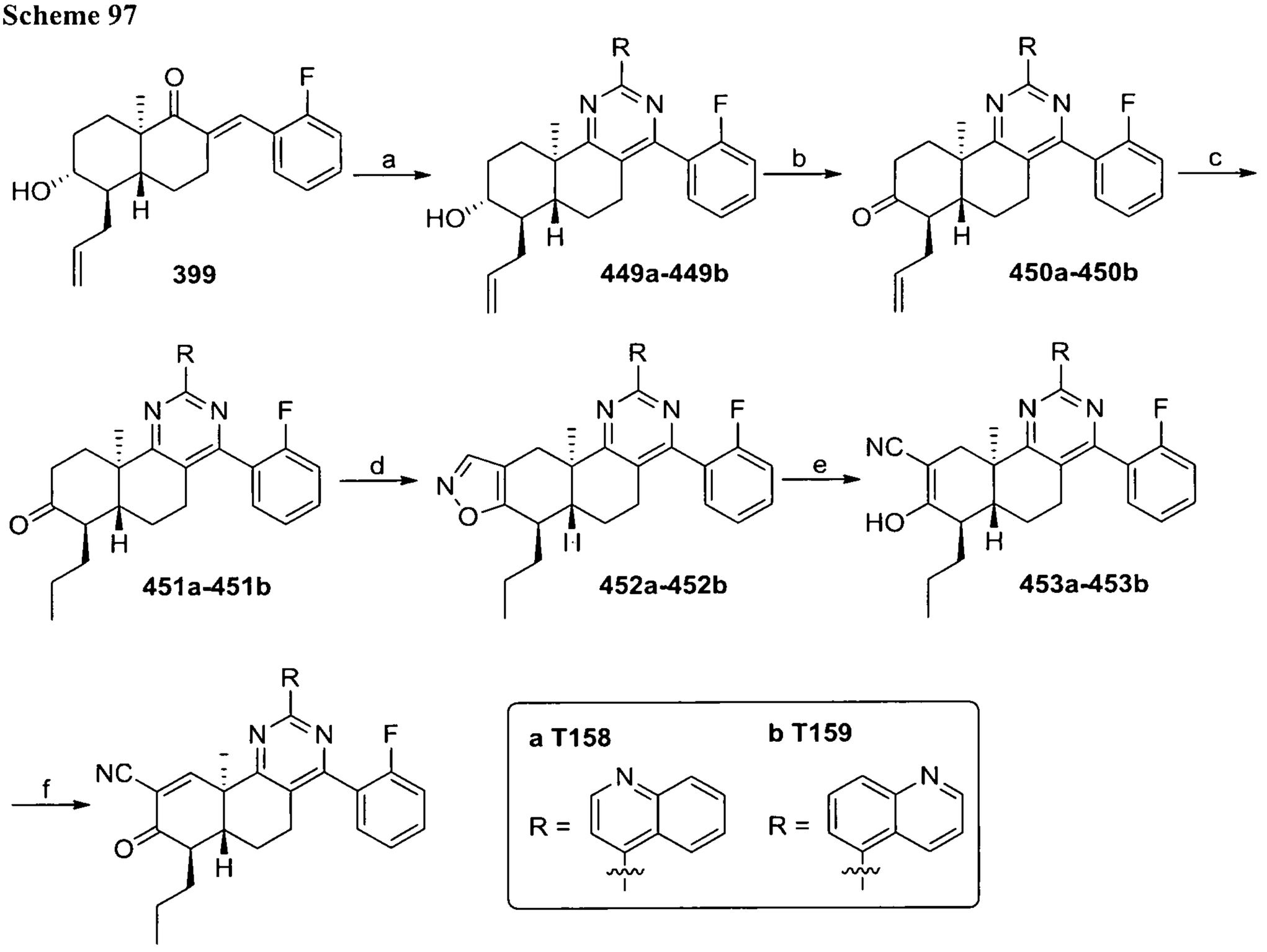
Reagents and conditions: a) $NaBH_4$, EtOH, 0 °C; b) Li/NH_3 (*l*), *t*-BuOH, THF, -78 °C; c) H_2, 10% Pd/C, EtOAc, 1 atm, rt; d) ethylene glycol, *p*-TsOH·H_2O, benzene, reflux, -H_2O; e) PDC, $MgSO_4$, CH_2Cl_2, rt; f) 2-F-PhCHO, KF/Al_2O_3, EtOH, rt; g) i) amidine hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; h) aq. 3 N HCl, THF, rt; i) i) HCO_2Et, NaOMe, MeOH, rt; ii) NH_2OH·HCl, EtOH, aq. 12 N HCl, 50 °C; j) K_2CO_3, MeOH, rt; k) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 96



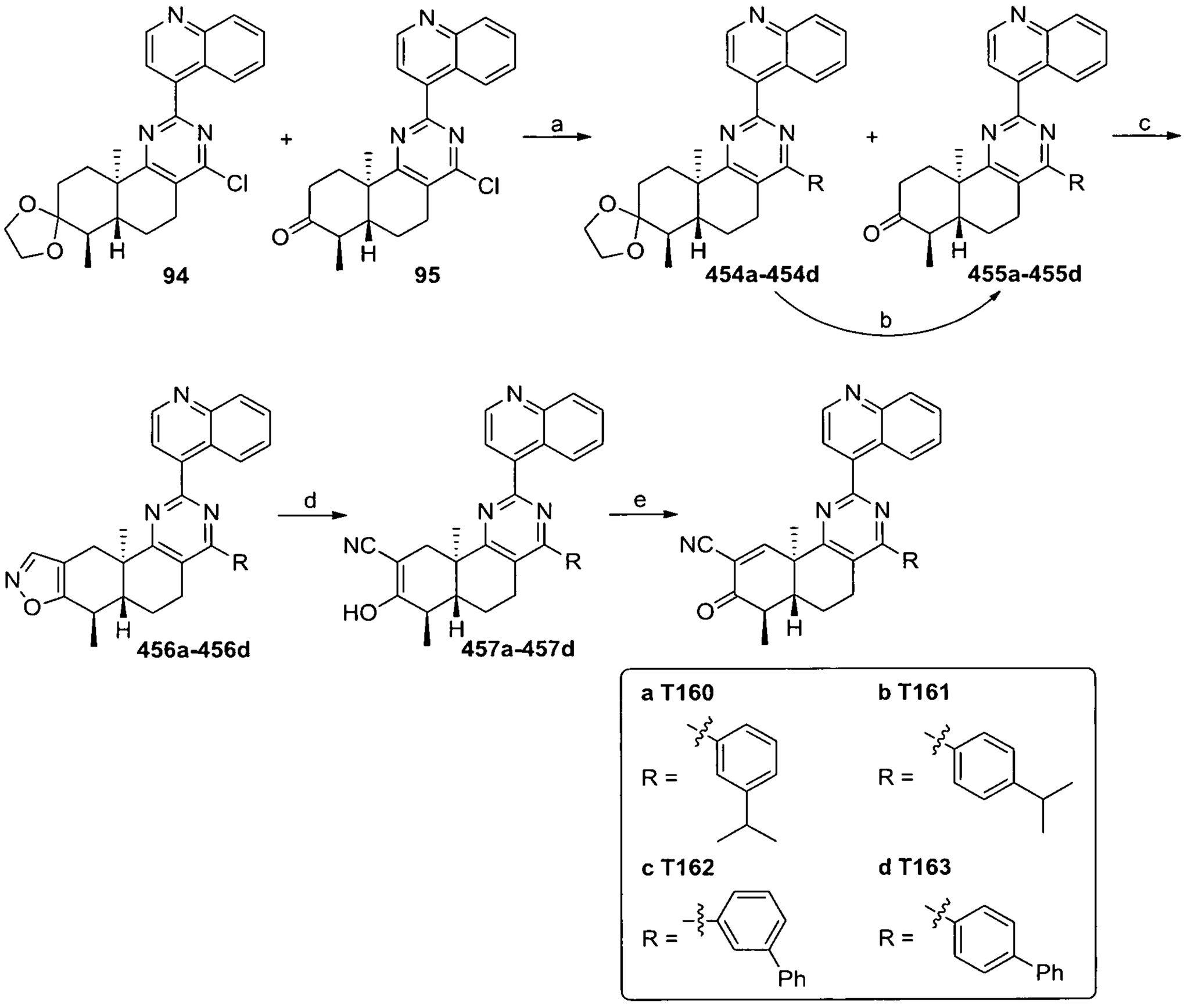
Reagents and conditions: a) *t*-BuOK, allyl bromide, THF, 0 °C; b) $NH_2OH{\cdot}HCl$, aq. 1N HCl, EtOH, 55 °C; c) i) *i*-Bu_3Al, CH_2I_2, CH_2Cl_2, rt; ii) NMO, OsO_4, acetone, H_2O, 0 °C to rt; d) NaOMe, MeOH, 55 °C; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 97



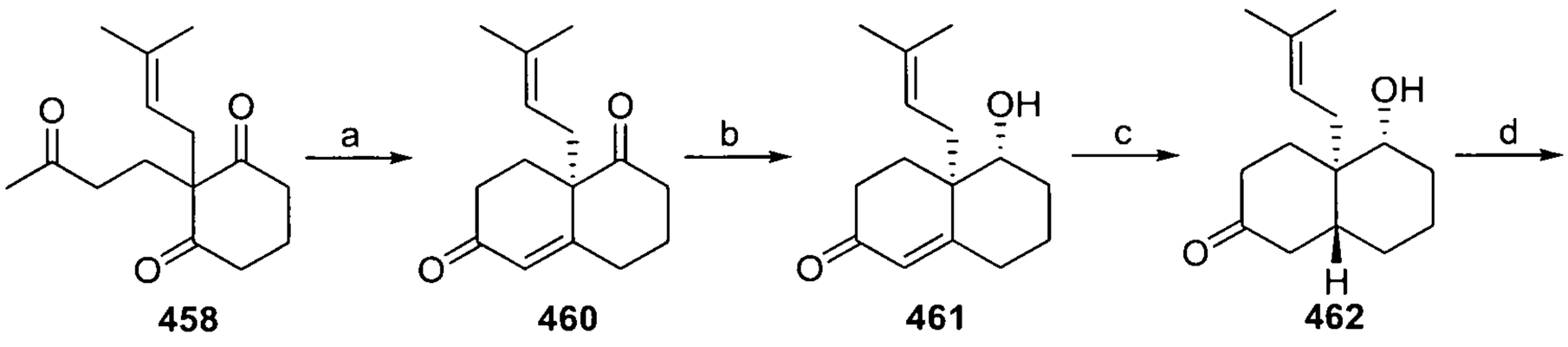
Reagents and conditions: a) i) amidine hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; b) Dess-Martin periodinane, CH_2Cl_2, rt; c) H_2, 10% Pd/C, EtOAc, rt; d) i) HCO_2Et, NaOMe, MeOH, 0 °C-rt; ii) aq. 6 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; e) NaOMe, MeOH, 55 °C; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

Scheme 98



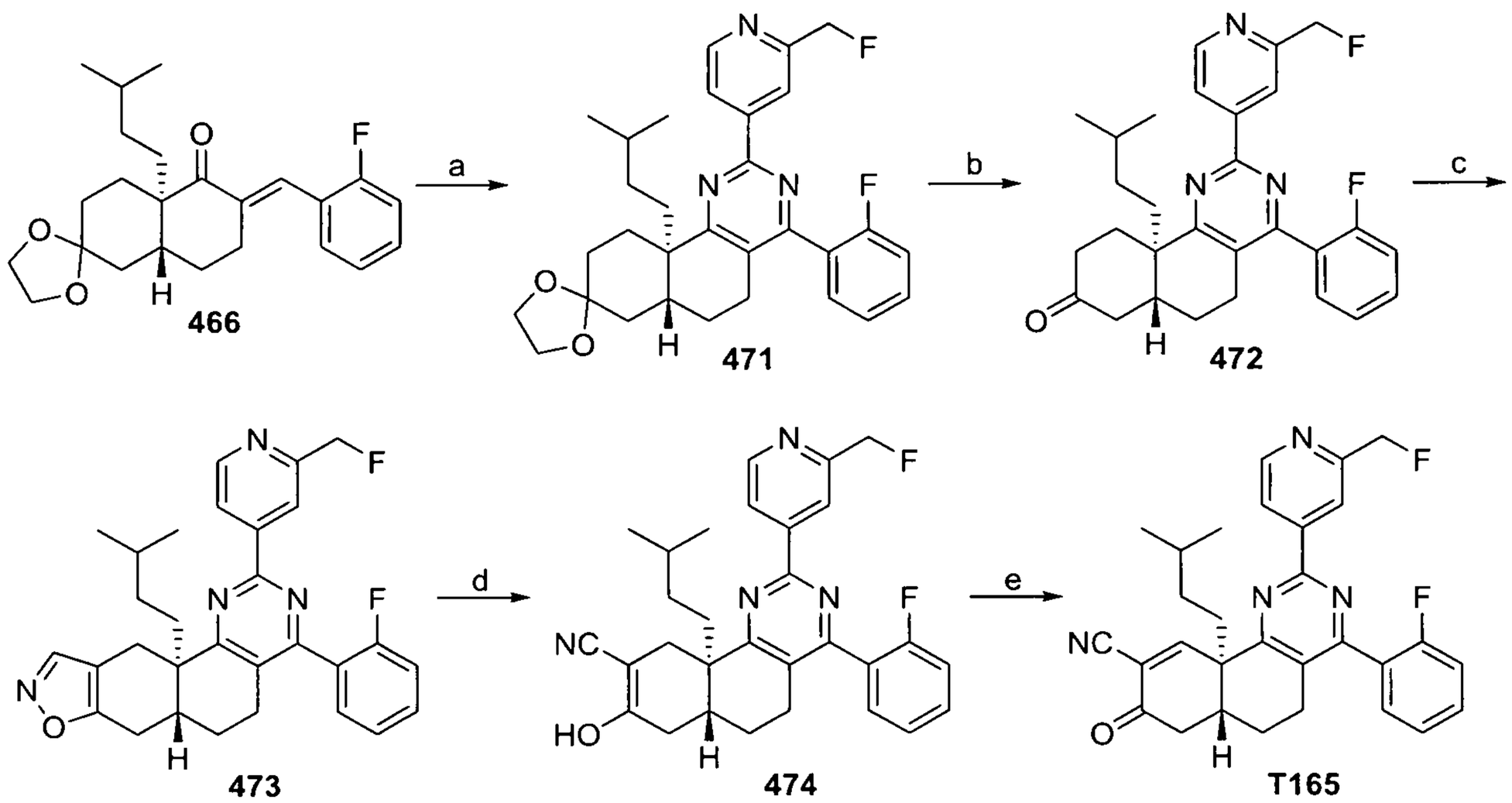
Reagents and conditions: a) arylboronic acid, $Pd(dppf)Cl_2$, K_2CO_3, 1,4-dioxane, 90 °C; b) aq. 3 N HCl, THF, rt; c) i) HCO_2Et, NaOMe, rt; ii) aq. 12 N HCl, $NH_2OH{\cdot}HCl$, EtOH, 55 °C; d) K_2CO_3, MeOH, rt; e) i) DBDMH, DMF, 0 °C, 2 h; ii) pyridine, 60 °C.

Scheme 99



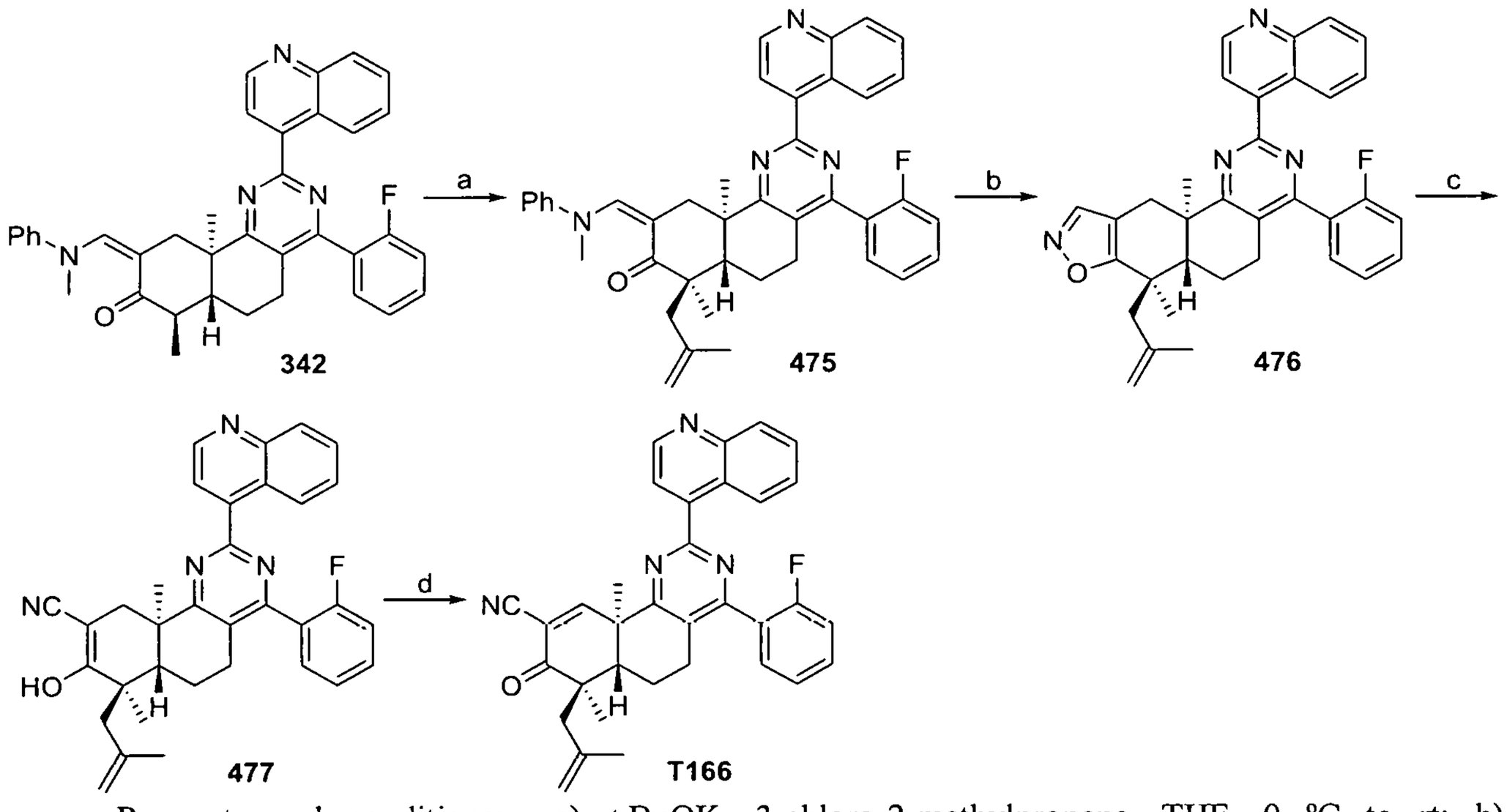
Reagents and conditions: a) **459**, benzoic acid, rt; b) $NaBH_4$, EtOH, 0 °C; c) Li/NH_3 (*l*), *t*-BuOH, THF, -78 °C; d) H_2, 10% Pd/C, EtOAc, 1 atm, rt; e) ethylene glycol, *p*-TsOH·H_2O, benzene, reflux, -H_2O; f) PDC, $MgSO_4$, CH_2Cl_2, rt; g) 2-F-PhCHO, KF/Al_2O_3, *i*-PrOH, rt; h) i) 4-quinolinecarboximidamide hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; i) aq. 3 N HCl, THF, rt to 50 °C; j) i) HCO_2Et, NaOMe, MeOH, rt; ii) NH_2OH·HCl, EtOH, aq. 6 N HCl, 55 °C; k) K_2CO_3, MeOH, rt; l) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 100



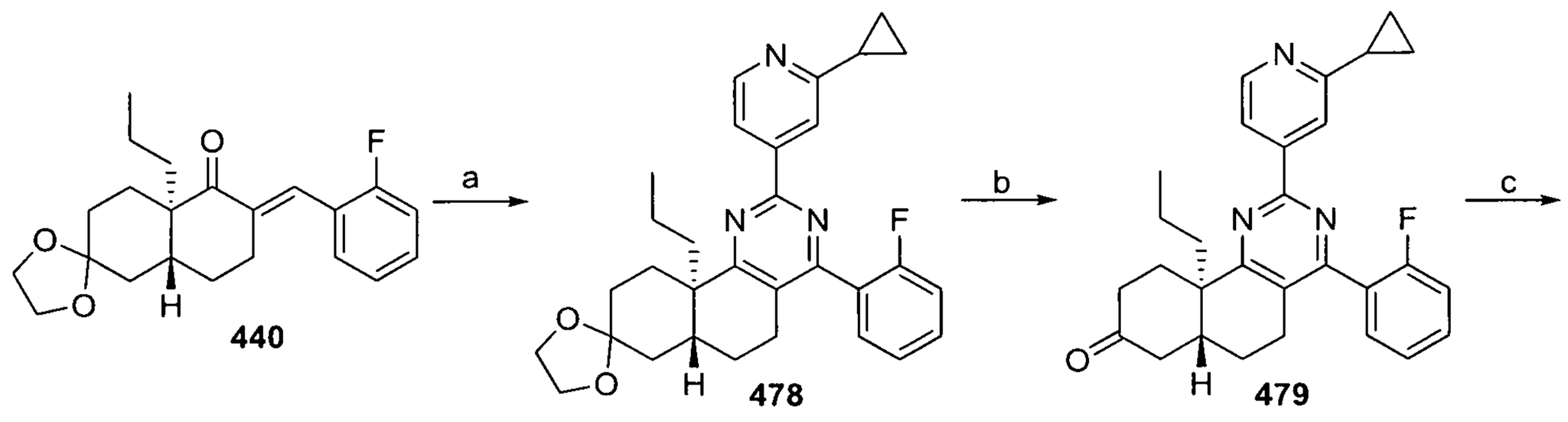
Reagents and conditions: a) i) amidine HCl, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; b) aq. HCl, THF, rt to 50 °C; c) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) aq. HCl, $H_2NOH \cdot HCl$, EtOH, 55 °C; d) K_2CO_3, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 101



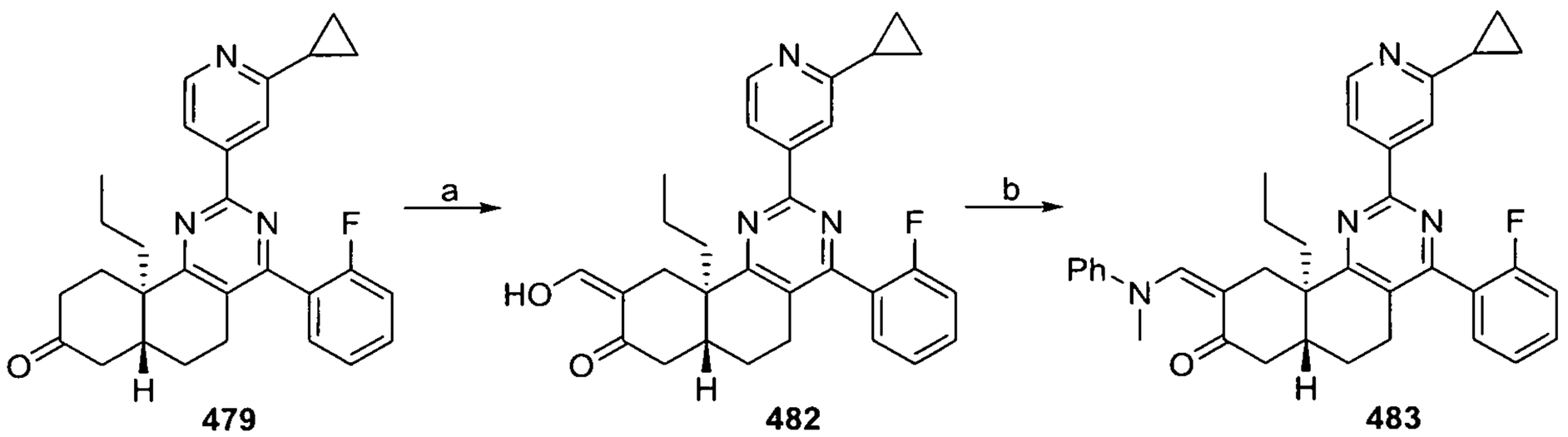
Reagents and conditions: a) *t*-BuOK, 3-chloro-2-methylpropene, THF, 0 °C to rt; b) $H_2NOH \cdot HCl$, aq. HCl, EtOH, 60 °C to rt; c) K_2CO_3, MeOH, rt; d) DDQ, toluene, rt.

Scheme 102



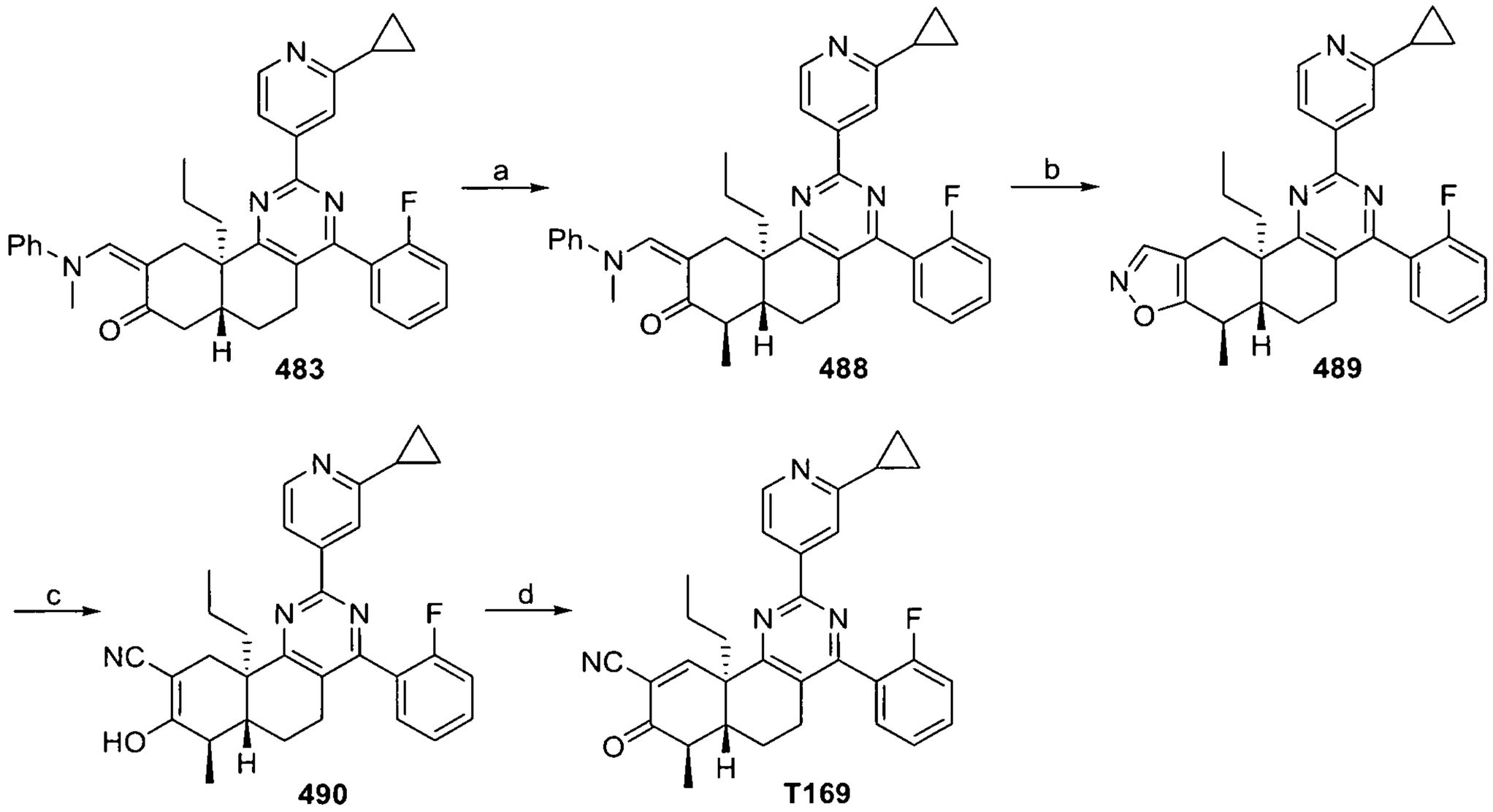
Reagents and conditions: a) i) 2-cyclopropylisonicotinimidamide hydrochloride, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; b) aq. 3 N HCl, THF, rt; c) i) HCO_2Et, NaOMe, MeOH, rt; ii) $NH_2OH \cdot HCl$, EtOH, aq. 12 N HCl, 50 °C; d) K_2CO_3, MeOH, rt; e) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 103



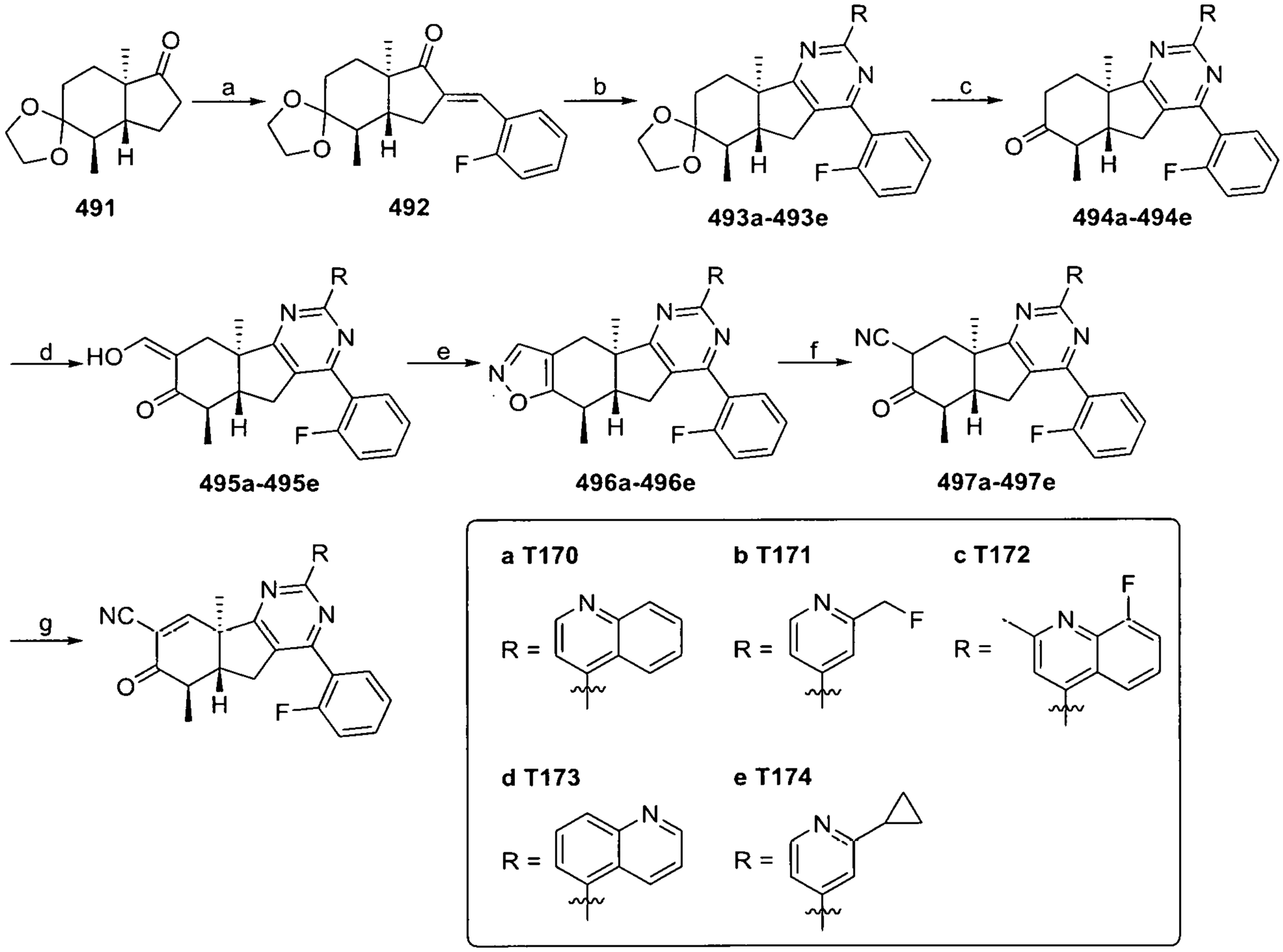
Reagents and conditions: a) HCO_2Et, NaOMe, MeOH, rt; b) N-methylaniline, 3 Å molecular sieves, *p*-TsOH, CH_2Cl_2, rt; c) i) LDA, cyclohexane, THF, 0 °C; ii) allyl bromide, 0 °C; d) $NH_2OH \cdot HCl$, 1N aq. HCl, EtOH, 55 °C; e) K_2CO_3, MeOH, rt; f) 10% Pd/C, H_2 (1 atm), EtOAc, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 104



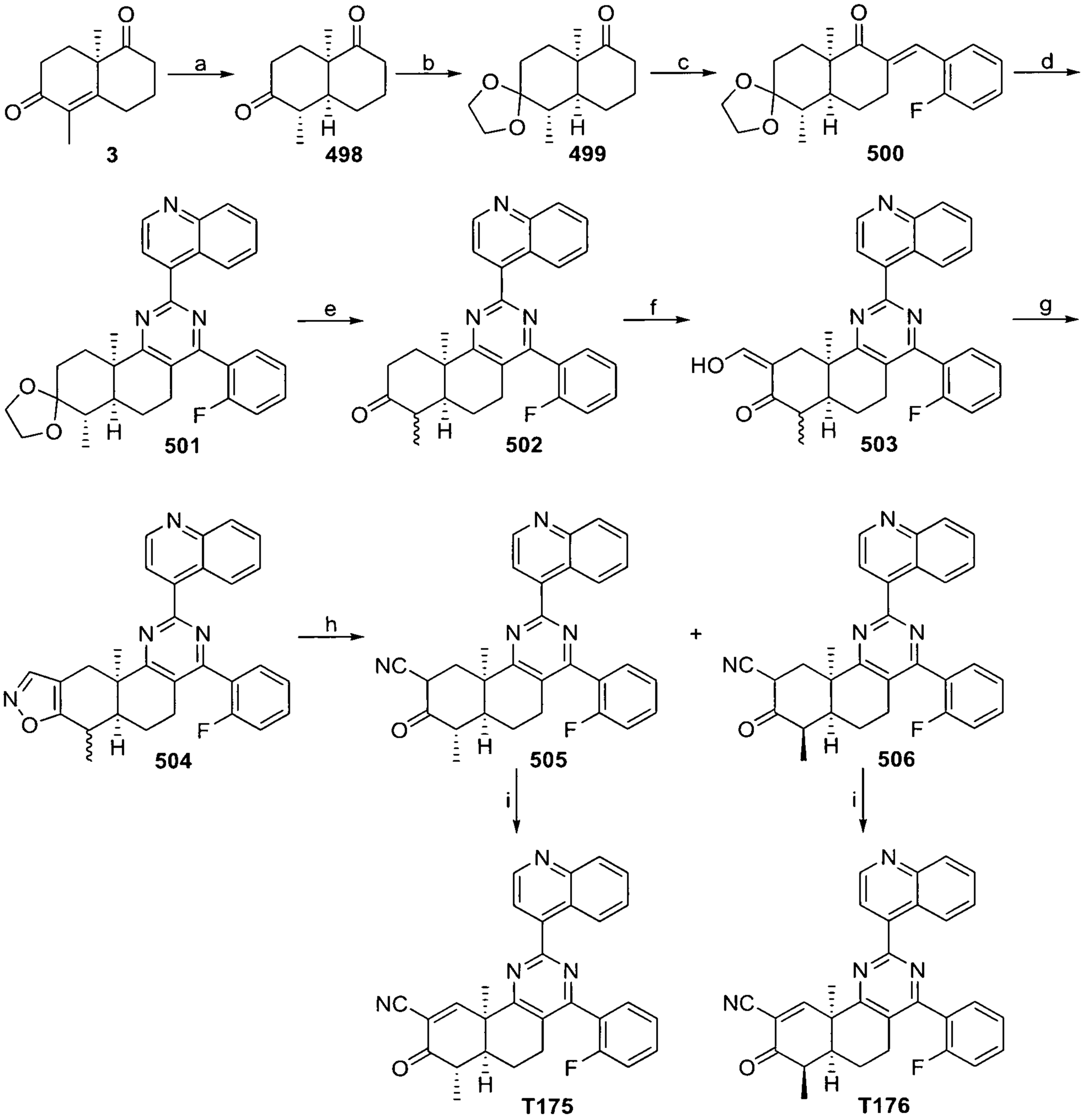
Reagents and conditions: a) i) LDA, cyclohexane, THF, 0 °C; ii) MeI, 0 °C; b) $NH_2OH \cdot HCl$, EtOH, 1 N aq. HCl, 55 °C; c) K_2CO_3, MeOH, rt; d) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 105



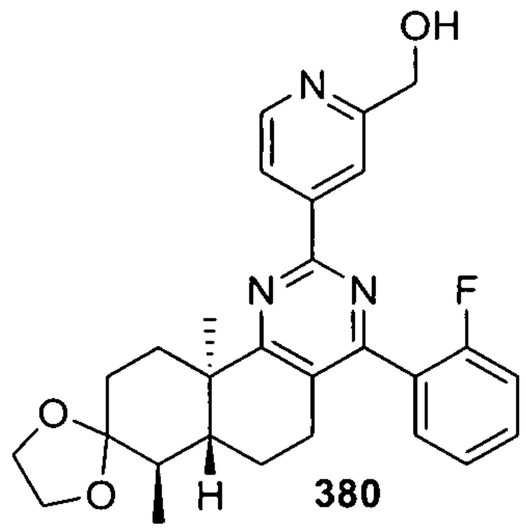
Reagents and conditions: a) 2-F-benzaldehyde, KF/Al_2O_3, EtOH, rt; b) i) amidine HCl, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; c) aq. HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, 12 N aq. HCl, EtOH, 55 °C; f) K_2CO_3, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 106

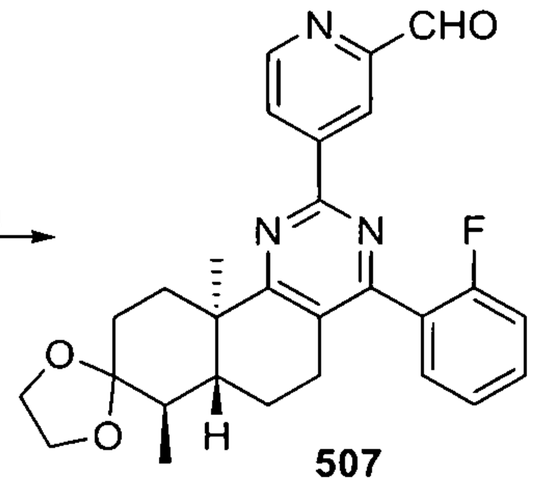


Reagents and conditions: a) H_2 (1 atm), 5% Pd/C, 95% aq. EtOH, rt; b) 2-ethyl-2-methyl-1,3-dioxolane, *p*-TsOH, ethylene glycol, 15 °C; c) 2-F-benzaldehyde, KF/Al_2O_3, EtOH, rt; d) i) amidine HCl, K_2CO_3, EtOH, reflux; ii) MnO_2, CH_2Cl_2, rt; e) aq. HCl, THF, rt; f) HCO_2Et, NaOMe, MeOH, rt; g) $NH_2OH \cdot HCl$, 12 N aq. HCl, EtOH, 55 °C; h) K_2CO_3, MeOH, rt; i) 1) DBDMH, DMF, 0 °C; 2) pyridine, 60 °C.

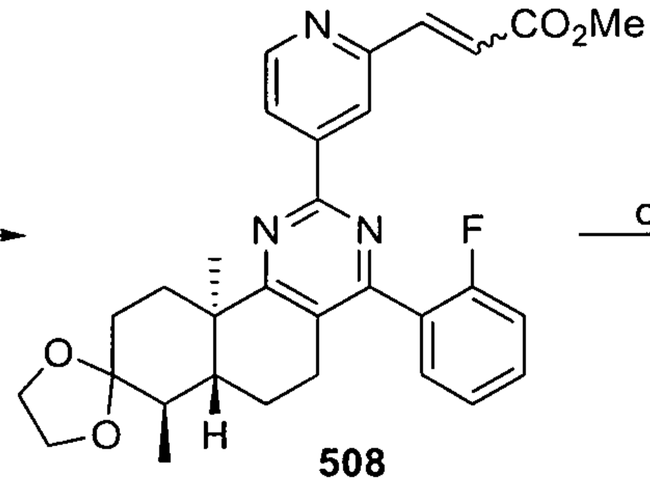
Scheme 107



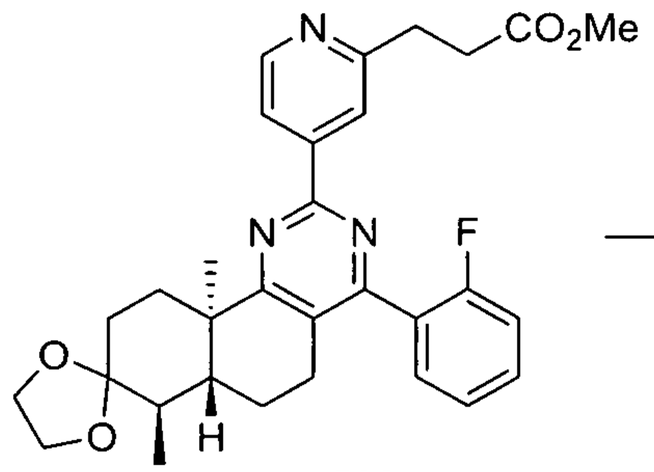
380



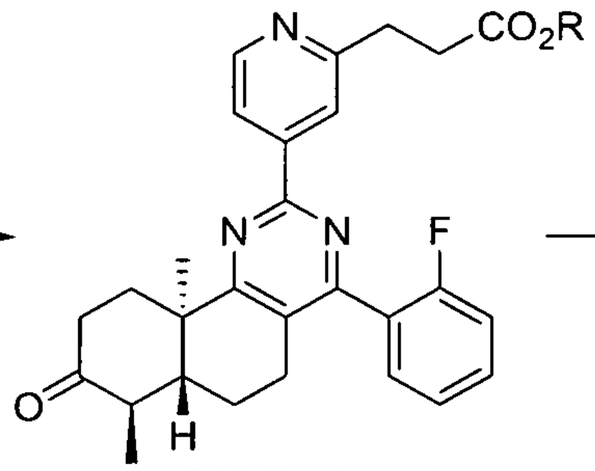
507



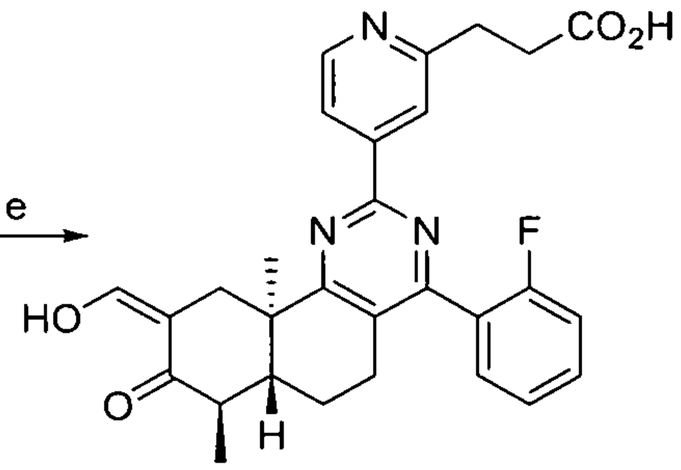
508



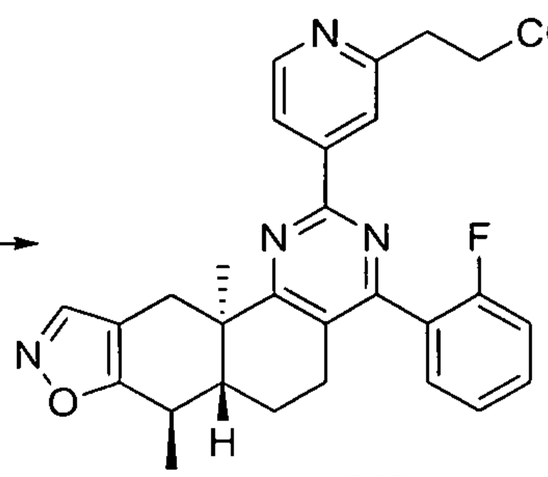
509



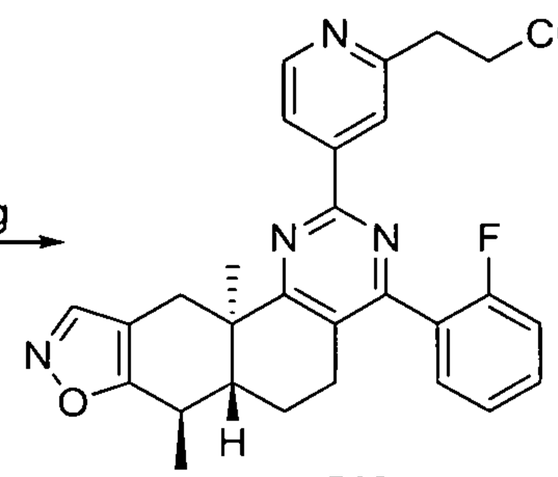
510 R = H or Me



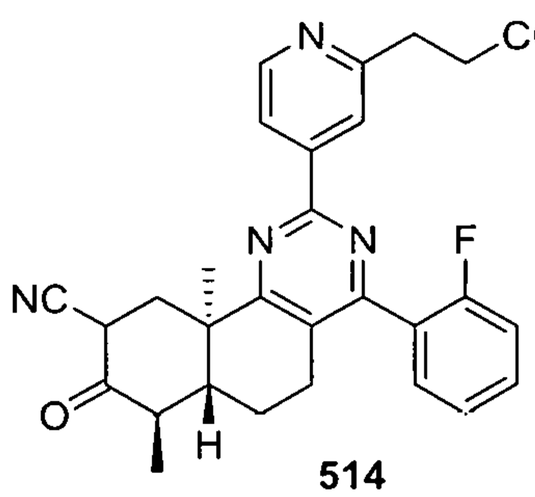
511



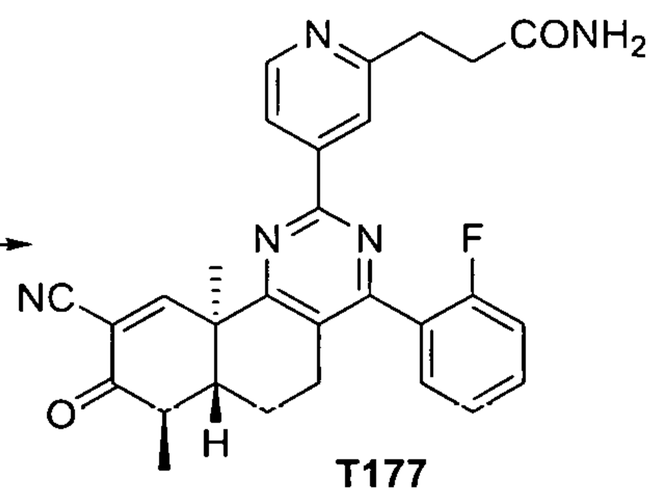
512



513



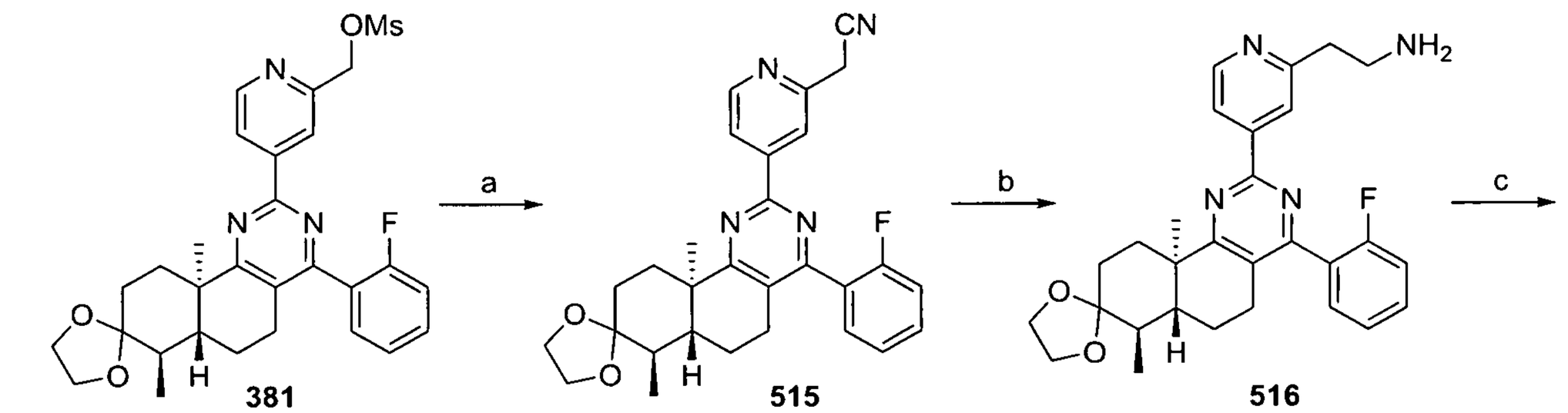
514



T177

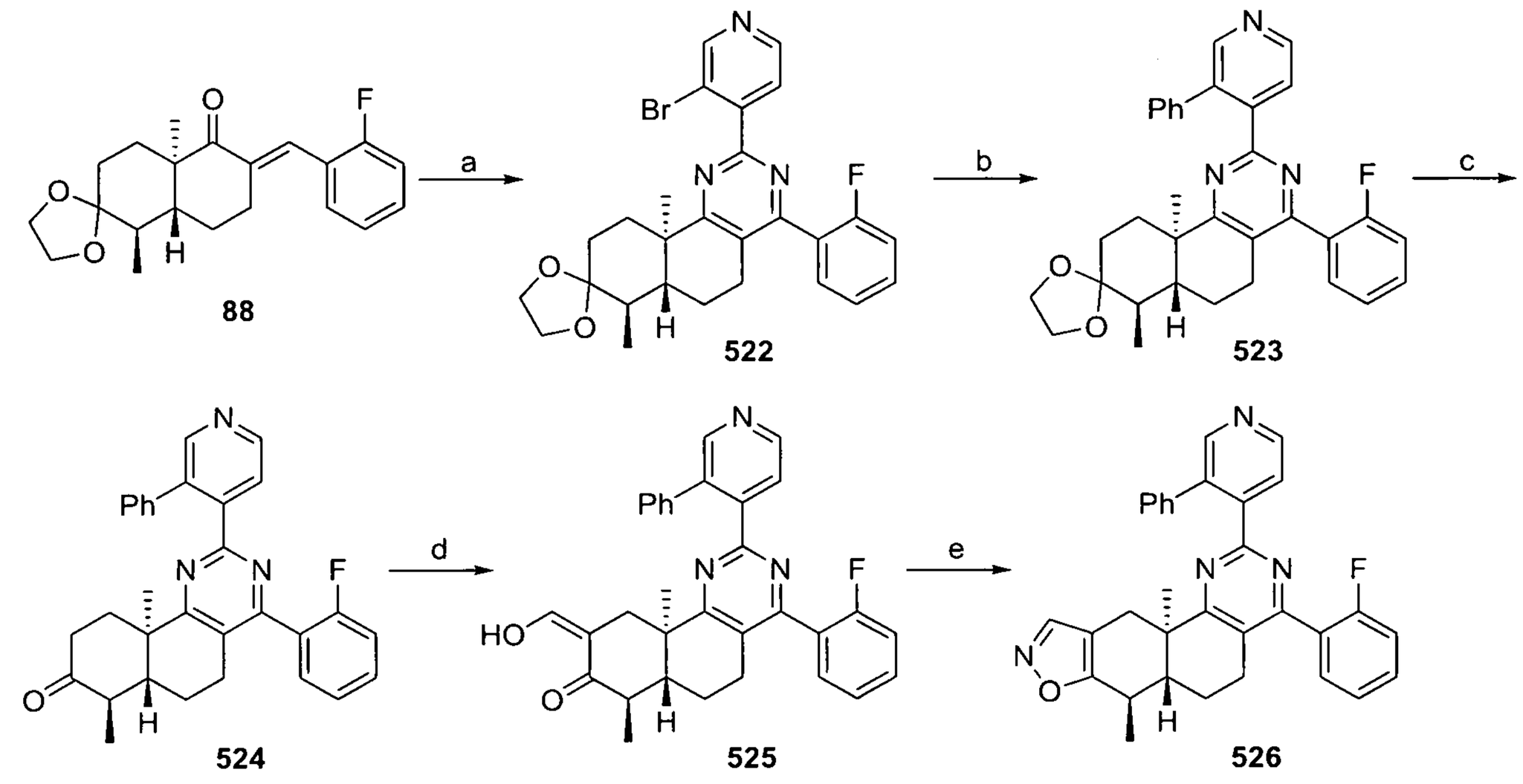
Reagents and conditions: a) MnO_2, CH_2Cl_2, rt; b) methyl (triphenylphosphoranylidene)acetate, benzene, rt; c) H_2 (1 atm), 10% Pd/C, EtOAc, rt; d) 3 N aq. HCl, THF, rt; e) HCO_2Et, NaOEt, EtOH, rt; f) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C to rt; g) NH_4Cl, $AlMe_3$, toluene, 0 °C to rt; h) K_2CO_3, MeOH, rt; i) 1) DBDMH, DMF, 0 °C; 2) pyridine, 60 °C.

Scheme 108



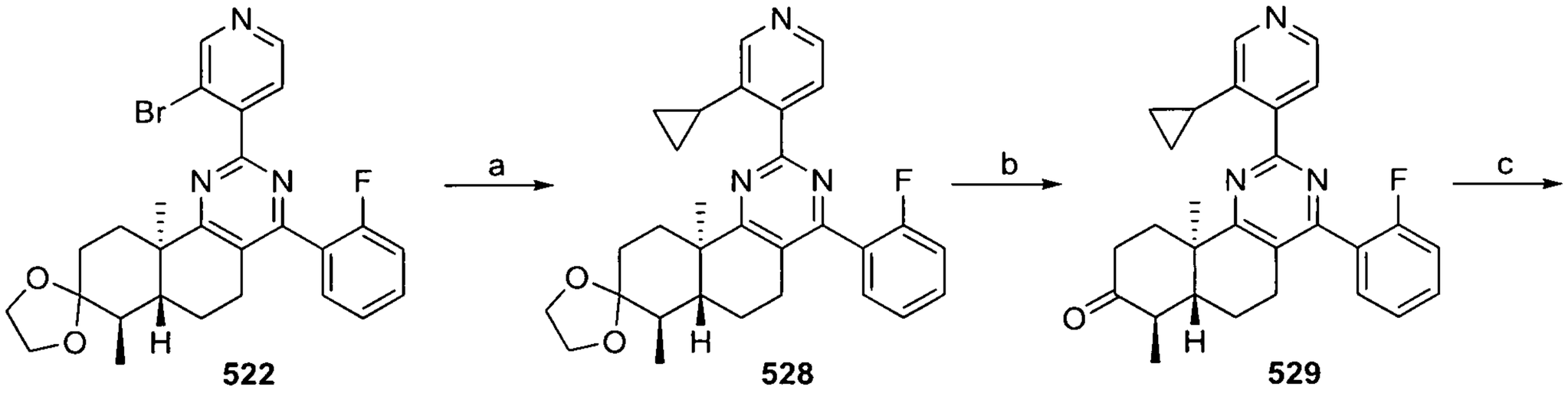
Reagents and conditions: a) KCN, 18-crown-6, MeCN, 50 °C; b) H_2 (1 atm), W2 Raney nickel, MeOH, rt; c) NaOAc, Ac_2O, rt; d) 3 N aq. HCl, THF, rt; e) N,N-dimethylformamide dimethylacetal, 100 °C; f) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C to rt; g) K_2CO_3, MeOH, rt; h) 1) DBDMH, DMF, 0 °C; 2) pyridine, 60 °C.

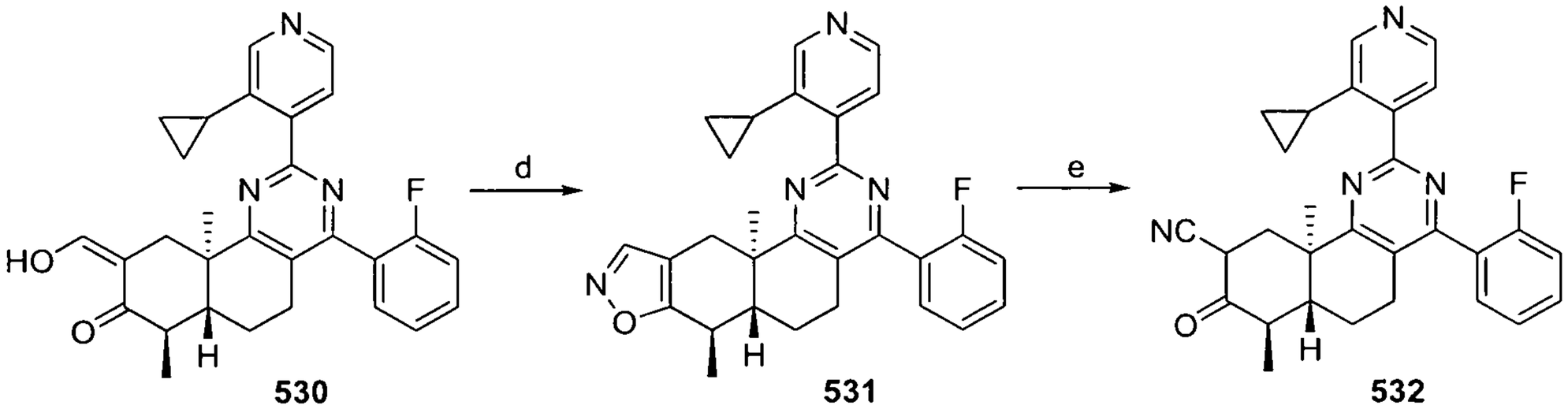
Scheme 109

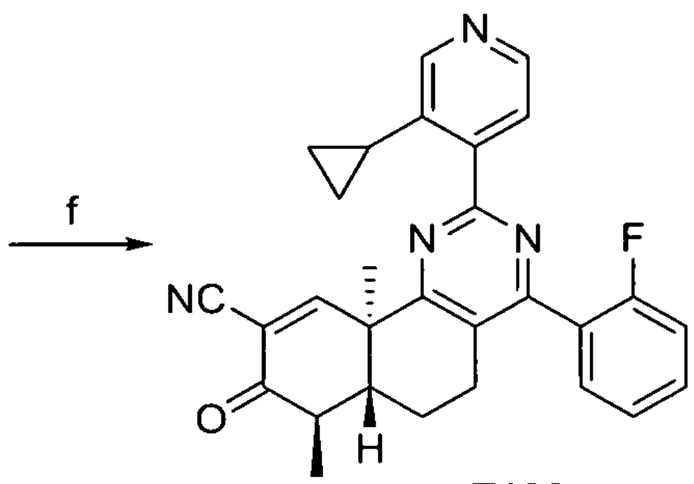


Reagents and conditions: a) i) 3-bromoisonicotinimidamide hydrochloride, K_2CO_3, EtOH, rt to 80 °C; ii) MnO_2, CH_2Cl_2, rt; b) $PhB(OH)_2$, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, DMF, 100 °C; c) aq. 3 N HCl, MeOH, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C to rt; f) K_2CO_3, MeOH, rt; g) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 110

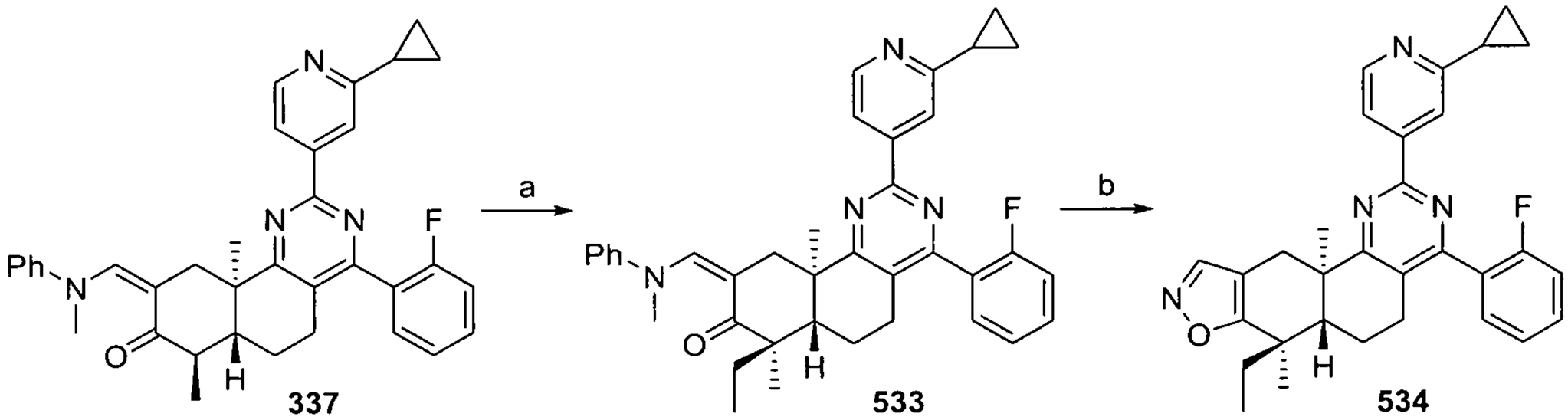






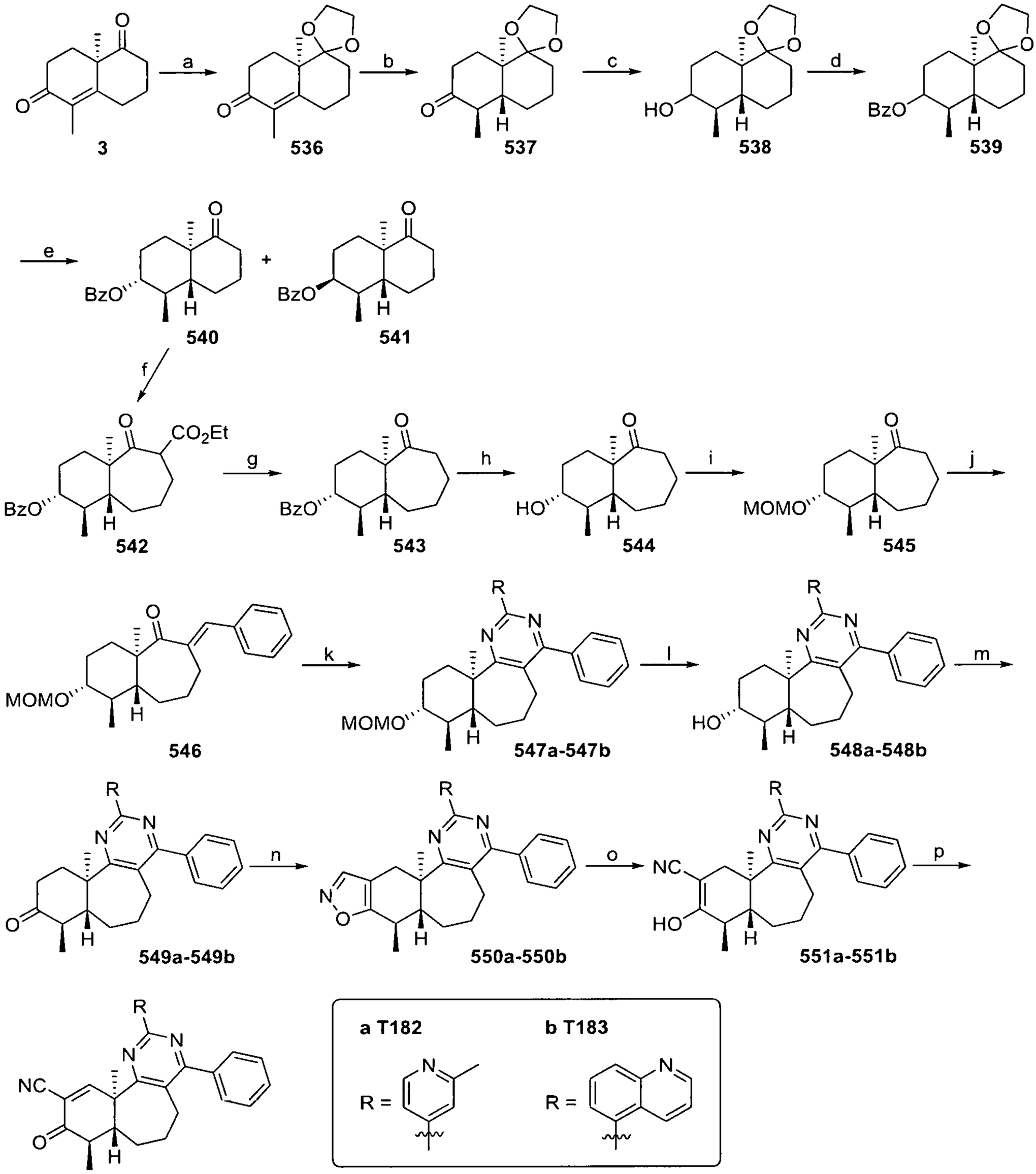
Reagents and conditions: a) potassium cyclopropyltrifluoroborate, K_3PO_4, $Pd(OAc)_2$, RuPhos, toluene, water, 100 °C; b) aq. 3 N HCl, MeOH, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH \cdot HCl$, AcOH, EtOH, 60 °C to rt; e) K_2CO_3, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C.

Scheme 111



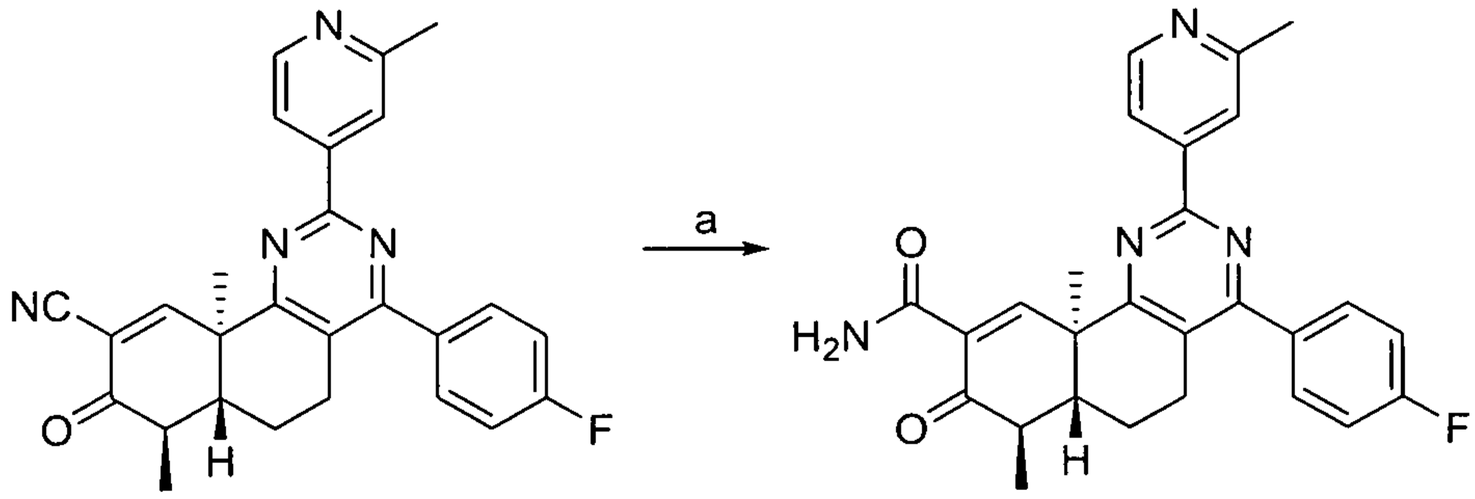
Reagents and conditions: a) *t*-BuOK, EtI, THF, 0 °C; b) $NH_2OH \cdot HCl$, 1 N aq. HCl, EtOH, 60 °C; c) K_2CO_3, MeOH, rt; d) i) DBDMH, DMF, 0 °C; ii) pyridine, DMF, 55 °C.

Scheme 112



Reagents and conditions: a) ethylene glycol, *p*-TsOH·H_2O, 15 °C; b) Li, NH_3 (liq.), H_2O, THF, -78 °C to -30 °C; c) $LiAlH_4$, Et_2O, -78 °C; d) PhCOCl, pyridine, CH_2Cl_2, 15 °C; e) 3 N aq. HCl, EtOH, 20 °C; f) ethyl diazoacetate, BF_3·OEt_2, Et_2O, 0 °C to 25 °C; g) LiI, H_2O, 2,4,6-collidine, 150 °C; h) 2 M aq. NaOH, EtOH, 15 °C; i) MOMCl, (*i*-Pr)$_2$EtN, CH_2Cl_2, rt; j) PhCHO, *t*-BuOK, *t*-BuOH, reflux; k) 2-methylisonicotinimidamide hydrochloride, *t*-BuOK, 1,4-dioxane, 200 °C, microwave; l) 12 N aq. HCl, THF, H_2O, rt; m) Dess-Martin periodinane, CH_2Cl_2, rt; n) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) 12 N aq. HCl, NH_2OH·HCl, EtOH, 55 °C; o) NaOMe, MeOH, 55 °C; p) i) DBDMH, DMF, 0 °C; ii) pyridine, 55 °C.

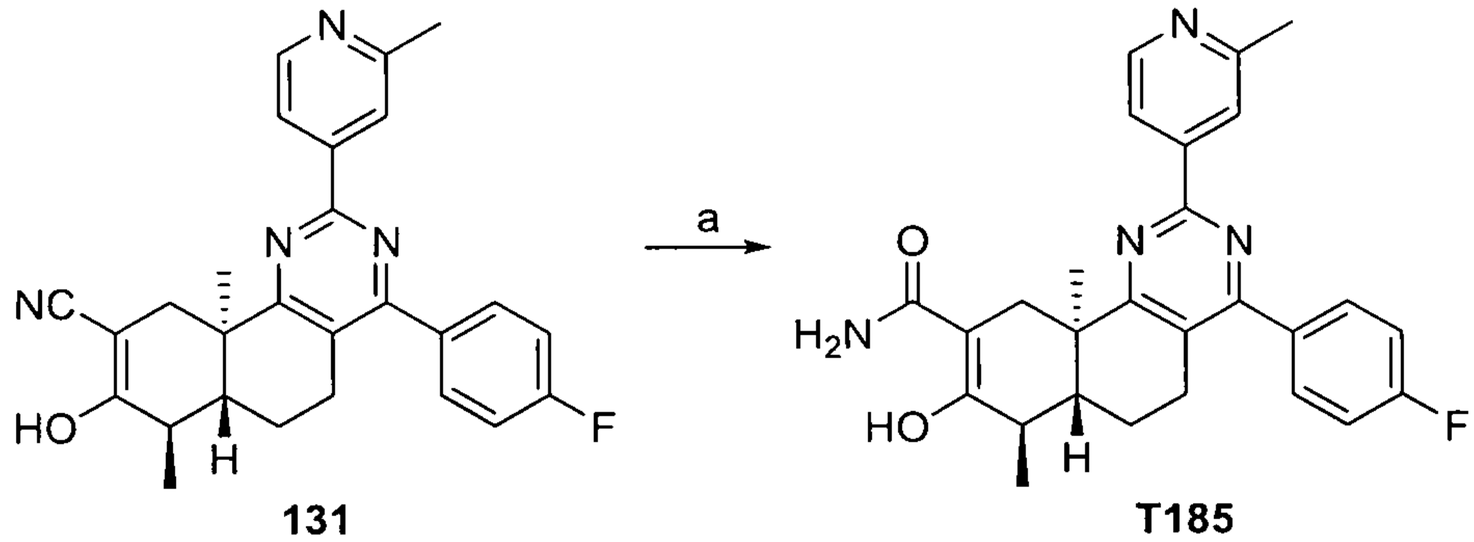
Scheme 113



T50 **T184**

Reagents and conditions: a) hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II), EtOH, H_2O, reflux.

Scheme 114



131 **T185**

Reagents and conditions: a) hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II), EtOH, H_2O, reflux.

ii. Characterization

I. General Information

Unless otherwise stated, commercially reagents were used as received, and all reactions were run under nitrogen atmosphere. Unless otherwise stated, the carboximidamides were prepared from the corresponding nitriles or carboxylic esters using the literature reported procedure (Garigipati, 1990). All solvents were of HPLC or ACS grade. Nuclear magnetic resonance (NMR) spectra were recorded on a *Varian Inova*-400 spectrometer at operating frequencies of 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform δ 7.26 ppm for ^{1}H NMR), and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet. Mass spectra were recorded on Waters Micromass ZQ or Agilent 6120 mass spectrometer.

II. Compound Characterization

Compound 2: Compound **1** (750.00 g, 5.95 mol) was dissolved in MeCN (8 L). Ethyl vinyl ketone (625.15 g, 7.43 mol) and uinolonemine (962.57 g, 9.51 mol) were added dropwise at 10 °C. The mixture was stirred for about 4 h, during which the temperature was kept below 25 °C. TLC (silica gel, petroleum ether/EtOAc = 3/1) indicated the starting material was consumed completely. MeCN was removed on a rotary evaporator, and the residue was diluted with ethyl acetate (8 L). The mixture was washed with aq. sat. KH_2PO_4 (8 L), and brine (5 L). The organic extract was dried over Na_2SO_4, and

filtered. The filter cake was washed with MeCN (1 L). The combined filtrate was concentrated to give compound **2** (1.20 kg, 96% yield) as a yellow oil. *m/z* = 211.1 (M+1).

Compound 3: A suspension of compound **2** (425.00 g, 2.02 mol), R-phenylalanine (267.11 g, 1.62 mol), (1*S*)-(+)-camphorsulfonic acid (281.72 g, 1.21 mol) in MeCN (2.1 L) was heated at 50 °C for 24 h, then at 60 °C for 48 h. The mixture was cooled to room temperature, and partitioned between EtOAc (3 L) and aq. sat. $NaHCO_3$ (3 L). The organic extract was washed with brine (3 L), dried over Na_2SO_4, filtered and concentrated. The residue was filtered through a silica gel pad, and eluted with 8/1 to 6/1 petroleum ether/EtOAc. The filtrate was concentrated to give crude compound **3** (388 g, quantitative yield).

Crude compound **3** (1.55 kg, 8.06 mol) was dissolved in MTBE (1.55 L). The mixture was cooled to 0 °C, and seeded with purified compound **3**. The mixture was kept at 0 °C for 2 h, then cooled to -10 °C and kept at the same temperature for 24 h. The precipitates were collected by filtration, and washed with cold MTBE (300 mL) to give compound **3** (792 g, 51% yield) as a white solid. *m/z* = 193.1 (M+1).

Compound 4: Compound **3** (200.00 g, 1.04 mol) was dissolved in EtOH (2.80 L) and cooled to -5 °C (internal temperature). Sodium borohydride (11.02 g, 291.30 mmol) was added portion wise over 30 min. The mixture was stirred for 2 h, during which the internal reaction temperature was controlled below 0 °C. TLC (silica gel, petroleum ether/EtOAc = 1/1) showed the start material was completely consumed. Acetic acid (96 mL, 1.68 mol) was added dropwise. After stirring for 30 min, the reaction mixture was concentrated on a rotary evaporator. EtOAc (1.5 L) was added and the mixture cooled to 0 °C. Aq. NaOH [made from NaOH (80 g, 2 mol) and ice-water (1 L)] was added to adjust pH to ~ 8. The solution was extracted with EtOAc (500 mL × 3). The combined organic extracts were washed with water (1 L), dried over Na_2SO_4, filtered through a silica gel pad and concentrated *in vacuo* to give compound **4** (204.20 g, quantitative yield) as a viscous colorless oil, which was used in the next step without further purification. *m/z* = 195.1 (M+1)

Compound 5: To a solution of compound **4** (204.20 g, ≤ 1.04 mol) in EtOAc (2.00 L) was added 5% palladium on barium sulfate (25.00 g). The mixture was stirred under hydrogen (15 psi) at 20 °C for 96 h. The catalyst was filtered off, and was washed with EtOAc (500 mL). The combined filtrate and wash was concentrated to give compound **5** (207 g, quantitative yield) as an oil, which was used in the next step without further purification.

Compound 6: A solution of compound **5** (207.00 g, ≤ 1.04 mol) in EtOH (2.00 L) was treated with aq. 3 N HCl (738.4 mL, 2.22 mol) at 20 °C. The mixture was stirred for 2 h, and concentrated. The residue was diluted with EtOAc (2.5 L), and washed with brine (2 × 1 L). The organic extract was concentrated, and the residue was filtered through a pad of silica gel (eluting with 10/1 to 8/1 petroleum ether/EtOAc) to give the crude product as a light yellow solid (203.25 g). The solid was dissolved in MTBE (1.22 L) at 40 °C, and *n*-pentane (1.22 mL) was added. The solution was cooled to room temperature, seeded with purified compound **6**, and kept at -20 °C for 16 h. The precipitates was

collected by filtration, washed with cold (-20 °C) mixture of MTBE and *n*-pentane (1/1, 100 mL) and dried under vacuum to give compound **6** (98 g, 48% yield) as a white solid. *m/z* = 197.2 (M+1)

Compound 7: To a solution of compound **6** (118.00 g, 601.15 mmol) in toluene (2.60 L) was added pyridinium *p*-toluenesulfonate (15.11 g, 60.13 mmol) and ethylene glycol (373.13 g, 6.01 mol) sequentially. The reaction was heated to reflux with Dean-Stark trap for 3 h. TLC (silica gel, petroleum ether/EtOAc = 3/1) showed the reaction was completed. The mixture was cooled to room temperature, and washed with water (2 × 1 L). The aqueous washes were extracted with toluene (2 × 1 L). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to give compound **7** (158.00 g, quantitative yield) as a glassy solid, which was used in the next step without further purification. *m/z* = 241.1 (M+1).

Compound 8: Sodium phosphate dibasic dodecahydrate (18.5 g, 51.66 mmol) and sodium tungstate uinolone (4.26 g, 12.90 mmol) were dissolved in aq. 30% H_2O_2 (175.49 g, 1.55 mol) to give a yellow solution. The solution was added dropwise to a solution of compound **7** (311.00 g, 1.29 mol) in *N,N*-dimethylacetamide (2.60 L) at 60 °C over 15 min. The mixture was heated at 90 °C for 3 h. TLC (silica gel, petroleum ether/EtOAc = 3:1) showed the reaction was completed. The mixture was cooled to room temperature, and diluted with EtOAc (5 L). The mixture was washed with aq. 10% Na_2SO_3 (2.5 L) and water (4 × 2 L) sequentially. The aqueous washes were extracted with EtOAc (2 × 1 L). The combined organic extracts were washed with water (2 × 1 L), dried over Na_2SO_4, filtered and concentrated. The crude product was dissolved in heptane (880 mL) at 40 °C. The solution was cooled at 4 °C for 1 h, seeded with purified compound **8**, and then kept at -20 °C for 20 h. The precipitates were collected by filtration, washed with cold (-20 °C) heptanes (300 mL), and dried under vacuum to give compound **8** (198.2 g, 64% yield) as a white solid. *m/z* = 239.2 (M+1).

Compound 9: To a stirring solution of compound **8** (10 g, 42.0 mmol) in THF (63 mL) was added dimethyl carbonate (35.3 mL, 419.3 mmol) and sodium hydride (60% dispersion in mineral oil, 5.1 g, 127.5 mmol) sequentially at room temperature under nitrogen. After addition, the mixture was heated at 80 °C for 16 h, and cooled to 0 °C. The reaction was quenched by dropwise addition of aq. sat. KH_2PO_4 and the mixture was extracted with EtOAc. The combined organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 10% acetone in hexanes) to give compound **9** (11.1 g, 89% yield) as a white solid. *m/z* = 297 (M+1).

Compound 10: Compound **9** (5.47 g, 18.47 mmol) was taken up in EtOH (65 mL). Thiourea (14 g, 183.9 mmol) and potassium *t*-butoxide (2.1 g, 18.71 mmol) were added. After heated at reflux for 16 h, the reaction mixture was concentrated, mixed with water (50 mL), and neutralized with aq. 3 N HCl. The precipitate was collected by filtration, washed with water, and dried under vacuum to give compound **10** (5.95 g, quantitative yield) as an off-white solid. *m/z* = 323 (M+1).

Compound 11: Compound **10** (5.95 g, 18.47 mmol) in chloroacetic acid (17.5 g, 185.2 mmol) was heated at 75 °C for 1 h. Water (15 mL) was added, and the mixture was heated at 100 °C for 4 h. Aq. conc. HCl (1.5 mL, 18 mmol) was added. The mixture was heated at 100 °C for another 16 h,

cooled, and diluted with ice water (50 mL). The precipitate was collected by filtration, and dried under vacuum to give compound **11** (4.8 g, 99% yield) as an off-white solid. *m/z* = 263 (M+1).

Compound 12: Compound **11** (4.8 g, 18.30 mmol) was taken up in $POCl_3$ (25 mL). *N*,*N*-Diisopropylethylamine (2.6 g, 20.12 mmol) was added. The mixture was heated at 90 °C for 16 h, cooled, and poured into ice. The precipitate was collected by filtration, washed with water, and dried under vacuum to give compound **12** (2.3 g, 42% yield) as a brown solid. *m/z* = 299 (M+1).

Compound 13: To a solution of compound **12** (100 mg, 0.33 mmol) in MeOH (3.3 mL) was added sodium methoxide (25 wt.% in MeOH, 0.10 mL, 0.43 mmol). The mixture was stirred at 50 °C for 1 h, and cooled to room temperature. Aq. 1 N HCl (0.5 mL, 0.5 mmol) was added, and the mixture was concentrated. The residue was partitioned between EtOAc and water, and the organic extract was washed with water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography (silica gel, eluting with 0% to 20% EtOAc in hexanes) to give compound **13** (82 mg, 83% yield) as a white solid. *m/z* = 295 (M+1).

Compound 14a: A mixture of compound **13** (150 mg, 0.509 mmol), 2-methoxypyridine-4-boronic acid (111 mg, 0.726 mmol), triphenylphosphine (50.8 mg, 0.194 mmol), potassium phosphate (324 mg, 1.528 mmol) in 1,2-dimethoxyethane (2.1 mL) and DMF (4.2 mL) was sparged with N_2 for 30 min. Palladium(II) acetate (22.9 mg, 0.102 mmol) was added and the nitrogen sparging was continued for another 10 min. The reaction mixture was heated at 95 °C for 2 h, cooled to room temperature, and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **14a** (136 mg, 73% yield) as a white solid. *m/z* = 368 (M+1).

Compound 15a: To a stirring solution of compound **14a** (130 mg, 0.354 mmol) in ethyl formate (3 mL, 37.3 mmol) was added sodium methoxide (25 wt.% solution in MeOH, 0.81 mL, 3.51 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature, and partitioned between aq. KH_2PO_4 and EtOAc. The organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in EtOH (3 mL) and water (0.3 mL), and treated with hydroxylamine hydrochloride (32 mg, 0.46 mmol). The mixture was heated overnight at 55 °C, cooled to room temperature, and concentrated. The residue was partitioned between water and EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated to give compound **15a** (95 mg, 68% yield) as a white solid. *m/z* = 393 (M+1).

Compound 16a: To a solution of compound **15a** (86.9 mg, 0.221 mmol) in a MeOH (2 mL) was added sodium methoxide (25 wt.% solution in MeOH, 0.3 mL, 1.30 mmol). The reaction mixture was stirred at 55 °C for 3 h, cooled and concentrated. The residue was partitioned between aq. KH_2PO_4 and EtOAc, and the organic extract was washed with brine, dried with $MgSO_4$, filtered and concentrated to give compound **16a** (58 mg, 67% yield) as a solid. *m/z* = 393 (M+1).

T2: To a solution of compound **16a** (56 mg, 0.143 mmol) in benzene (14 mL) was added DDQ (42 mg, 0.186 mmol) at room temperature. The reaction mixture was refluxed for 3 h, cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, eluting with

0% to 40 % EtOAc in hexanes) to give compound **T2** (28 mg, 50% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.32 (m, 1H), 7.89 (m, 1H), 7.77 (m, 1H), 4.11 (s, 3H), 4.03 (s, 3H), 2.89 (dd, J = 6.7, 18.7 Hz, 1H), 2.62 (m, 2H), 2.15 (m, 2H), 1.78 (m, 1H), 1.46 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H); *m/z* = 391 (M+1).

Compound 14b: A mixture of Compound **13** (150 mg, 0.509 mmol), 2-methylpyridine-4-boronic acid pinacol ester (168 mg, 0.767 mmol), triphenylphosphine (50.8 mg, 0.194 mmol), potassium phosphate (324 mg, 1.53 mmol) in 1,2-dimethoxyethane (2.1 mL) and DMF (4.2 mL) was sparged with nitrogen for 30 min. Palladium(II) acetate (22.9 mg, 0.102 mmol) was added and the nitrogen sparging was continued for another 10 min. The reaction mixture was heated at 95 °C for 16 h, cooled to room temperature, and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 0% to 40 % EtOAc in hexanes) to give compound **14b** (140 mg, 78% yield) as a white solid. *m/z* = 352 (M+1).

Compound 15b: To a stirring solution of compound **14b** (130 mg, 0.370 mmol) in ethyl formate (3 mL, 37.3 mmol) was added sodium methoxide (25 wt.% solution in MeOH, 0.85 mL, 3.68 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature, and partitioned between aq. KH_2PO_4 and EtOAc. The organic extract was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in EtOH (4 mL) and water (0.4 mL), and treated with hydroxylamine hydrochloride (33.5 mg, 0.482 mmol). The mixture was heated overnight at 55 °C, cooled to room temperature, and concentrated. The residue was partitioned between water and EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated to give compound **15b** (98 mg, 70% yield) as a white solid. *m/z* = 377 (M+1).

Compound 16b: To a solution of compound **15b** (90 mg, 0.239 mmol) in a MeOH (2 mL) was added sodium methoxide (25 wt.% solution in MeOH, 0.33 mL, 1.43 mmol). The reaction mixture was stirred at 55 °C for 3 h, cooled and concentrated. The residue was partitioned between aq. KH_2PO_4 and EtOAc, and the organic extract was washed with brine, dried with $MgSO_4$, filtered and concentrated to give compound **16b** (66 mg, 73% yield) as a pale yellow solid. *m/z* = 377 (M+1).

Compound T3: To a solution of compound **16b** (60 mg, 0.159 mmol) in benzene (14 mL) was added DDQ (47 mg, 0.207 mmol) at room temperature. The reaction mixture was refluxed for 3 h, cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60 % EtOAc in hexanes) to give compound **T3** (22 mg, 37% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.66 (d, J = 5.2 Hz, 1H), 8.14 (s, 1H), 8.10 (d, J = 5.1 Hz, 1H), 4.13 (s, 3H), 2.89 (dd, J = 6.7, 18.8 Hz, 1H), 2.71 (s, 3H), 2.61 (m, 2H), 2.16 (m, 2H), 1.77 (m, 1H), 1.47 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 375 (M+1).

Compound 14c: Compound **13** (50 mg, 0.17 mmol), 3-picoline-4-boronic acid (35 mg, 0.26 mmol), triphenylphosphine (17 mg, 0.065 mmol), potassium phosphate (108 mg, 0.51 mmol) and palladium acetate (7.6 mg, 0.034 mmol) in 1,2-dimethoxyethane (1.4 mL) and DMF (0.7 mL) in a microwave vial were sparged with nitrogen for 5 min. The vial was sealed, and heated in Biotage® microwave synthesizer at 100 °C for 5 h. The mixture was cooled to room temperature, filtered through a

silica gel plug, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **14c** (58 mg, 97% yield) as a yellow foamy solid. *m/z* = 352 (M+1).

Compound 15c: To a stirred solution of compound **14c** (80 mg, 0.23 mmol) in ethyl formate (0.55 mL) was added sodium methoxide (25 wt.% in methanol, 0.78 mL, 3.38 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.57 mL, 3.42 mmol), EtOH (2.3 mL), and hydroxylamine hydrochloride (24 mg, 0.35 mmol) were added sequentially. The mixture was heated at 55 °C for 4 h. EtOAc was added. The mixture was washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **15c** (63 mg, 74% yield) as a white foamy solid. *m/z* = 377 (M+1).

Compound 16c: Compound **15c** (55 mg, 0.15 mmol) was dissolved in MeOH (1.5 mL). Sodium methoxide (25 wt.% in methanol, 50 μL, 0.22 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to rt. EtOAc was added. The mixture was washed with aq. 10% KH_2PO_4. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **16c** (48 mg, 87% yield) as a white solid. *m/z* = 377 (M+1).

T4: Compound **16c** (38 mg, 0.10 mmol) was dissolved in toluene (2 mL) and benzene (1 mL). DDQ (25 mg, 0.11 mmol) was added. The mixture was heated at 85 °C for 1 h, and was cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **T4** (22 mg, 58% yield) as an off-white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.60 (m, 2H), 7.91 (d, J = 5.0 Hz, 1H), 4.08 (s, 3H), 2.90 (dd, J = 6.0, 18.8 Hz, 1H), 2.67 (s, 3H), 2.65 (m, 2H), 2.16 (m, 2H), 1.78 (m, 1H), 1.47 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 375 (M+1).

Compound 14d: Compound **13** (150 mg, 0.51 mmol), pyridine-4-boronic acid (93 mg, 0.76 mmol), triphenylphosphine (51 mg, 0.19 mmol), potassium phosphate (324 mg, 1.52 mmol) and palladium acetate (22 mg, 0.10 mmol) in 1,2-dimethoxyethane (2.1 mL) and DMF (1.1 mL) in a microwave vial were sparged with nitrogen for 5 min. The vial was sealed, and heated in Biotage® microwave synthesizer at 100 °C for 5 h. The mixture was cooled to room temperature, filtered through a silica gel plug, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **14d** (155 mg, 90% yield) as a white foamy solid. *m/z* = 338 (M+1).

Compound 15d: To a stirred solution of compound **14d** (90 mg, 0.27 mmol) in ethyl formate (0.64 mL) was added sodium methoxide (25 wt.% in methanol, 0.93 mL, 4.03 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.67 mL, 4.02 mmol),

EtOH (2.5 mL), and hydroxylamine hydrochloride (28 mg, 0.40 mmol) were added sequentially. The mixture was heated at 55 °C for 3 h. EtOAc was added. The mixture was washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **15d** (63 mg, 65% yield). *m/z* = 363 (M+1).

Compound 16d: Compound **15d** (63 mg, 0.17 mmol) was dissolved in MeOH (1.7 mL). Sodium methoxide (25 wt.% in methanol, 60 μL, 0.26 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to rt. EtOAc was added. The mixture was washed with aq. 10% KH_2PO_4. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **16d** (68 mg, quantitative yield) as a white solid. *m/z* = 363 (M+1).

T5: Compound **16d** (60 mg, 0.17 mmol) was dissolved in benzene (3.3 mL). DDQ (41 mg, 0.18 mmol) was added. The mixture was heated at 85 °C for 40 min, and was cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **T5** (30 mg, 50% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.79 (m, 2H), 8.30 (m, 2H), 4.14 (s, 3H), 2.90 (dd, J = 5.9, 19.1 Hz, 1H), 2.63 (m, 2H), 2.15 (m, 2H), 1.77 (dq, J = 6.8, 13.5 Hz, 1H), 1.47 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H); *m/z* = 361 (M+1).

Compound 14e: Compound **13** (50 mg, 0.17 mmol), 2-fluoropyridine-4-boronic acid (36 mg, 0.26 mmol), triphenylphosphine (17 mg, 0.065 mmol), potassium phosphate (108 mg, 0.51 mmol) and palladium acetate (8 mg, 0.036 mmol) were weighed in a vial, and kept under vacuum. 1,2-dimethoxyethane (0.73 mL) and DMF (0.37 mL) (sparged with nitrogen for 5 min) were added. The vial was filled with nitrogen, and was heated in Biotage® microwave synthesizer at 100 °C for 100 min. The mixture was cooled to room temperature, filtered through a silica gel plug, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% EtOAc in hexanes) to give compound **14e** (58 mg, 96% yield) as a white solid. *m/z* = 356 (M+1).

Compound 15e: To a stirred solution of compound **14e** (53 mg, 0.15 mmol) in ethyl formate (0.36 mL) was added sodium methoxide (25 wt.% in methanol, 0.52 mL, 2.25 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.37 mL, 2.22 mmol), EtOH (1.5 mL), and hydroxylamine hydrochloride (16 mg, 0.23 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h. EtOAc was added. The mixture was washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 5% EtOAc in CH_2Cl_2) to give compound **15e** (37 mg, 65% yield) as a white solid. *m/z* = 381 (M+1).

Compound 16e: Compound **15e** (37 mg, 0.097 mmol) was dissolved in MeOH (2 mL). Potassium carbonate (68 mg, 0.49 mmol) was added. The reaction mixture was stirred at room

temperature for 16 h. EtOAc and aq. 1 N HCl (1 mL) were added. The mixture was extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 5% EtOAc in CH_2Cl_2) to give compound **16e** (32 mg, 86% yield) as a white foamy solid. *m/z* = 381 (M+1).

T6: Compound **16e** (27 mg, 0.071 mmol) was dissolved in benzene (1.5 mL). DDQ (18 mg, 0.079 mmol) was added. The mixture was heated at 85 °C for 2 h, and was cooled to room temperature. The reaction mixture was purified by flash chromatography (silica gel, eluting with 0% to 15% acetone in hexanes) to give compound **T6** (8 mg, 30% yield) as a yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.38 (d, J = 5.2 Hz, 1H), 8.21 (td, J = 1.6, 5.2 Hz, 1H), 7.93 (s, 1H), 4.14 (s, 3H), 2.91 (dd, J = 6.2, 18.9 Hz, 1H), 2.64 (m, 2H), 2.16 (m, 2H), 1.79 (m, 1H), 1.47 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 379 (M+1).

Compound 17: Compound **13** (100 mg, 0.34 mmol), pyridine-3-boronic acid (62 mg, 0.50 mmol), triphenylphosphine (34 mg, 0.13 mmol), potassium phosphate (216 mg, 1.02 mmol) and palladium acetate (15 mg, 0.067 mmol) in 1,2-dimethoxyethane (1.4 mL) and DMF (0.7 mL) in a microwave vial were sparged with nitrogen for 5 min. The vial was sealed, and heated in Biotage® microwave synthesizer at 100 °C for 5 h. The mixture was cooled to room temperature, filtered through a silica gel plug, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give compound **17** (106 mg, 92% yield) as a white foamy solid. *m/z* = 338 (M+1).

Compound 18: To a solution of compound **17** (95 mg, 0.28 mmol) in THF (1.4 mL) was added lithium bis(trimethylsilyl)amide solution (1 M in THF, 0.42 mL, 0.42 mmol) at -78 °C. After the mixture was stirred at -78 °C for 10 min, phenylselenyl chloride (82 mg, 0.43 mmol) in THF (1.4 mL) was added. The mixture was stirred at -78 °C for an additional 1.5 h. Aq. sat. NH_4Cl was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give partially purified product. The product was dissolved in EtOAc (4 mL) and THF (1.2 mL). Hydrogen peroxide (30 wt.% solution in water, 0.14 mL, 1.37 mmol) was added at room temperature. The reaction was stirred for 1 h. Aq. 10% Na_2SO_3 was added. The mixture was extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give compound **18** (46 mg, 48% yield) as a white solid. m/z = 336 (M+1).

Compound 19: A solution of compound **18** (36 mg, 0.11 mmol) and iodine (27 mg, 0. 11 mmol) in pyridine (0.5 mL) was heated at 80 °C for 16 h, and was cooled to rt. EtOAc was added. The mixture was washed with aq. 10% Na_2SO_3, aq. 1 N HCl and water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **19** (23 mg, 46% yield) as a yellow solid. *m/z* = 462 (M+1).

T7: A mixture of compound **19** (21 mg, 0.046 mmol), zinc cyanide (17 mg, 0.14 mmol) in DMF (0.5 mL) was sparged with nitrogen for 2 min. Tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.005 mmol) was added. The nitrogen sparging was continued for another 2 min. The reaction was heated at

80 °C under nitrogen for 1 h, and was cooled to room temperature. EtOAc was added. The mixture was filtered through a pad of Celite®, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes to give compound **T7** (2.1 mg, 13% yield) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, J = 2.0 Hz, 1H), 8.96 (s, 1H), 8.72 (m, 2H), 7.44 (m, 1H), 4.12 (s, 3H), 2.88 (dd, J = 6.0, 18.8 Hz, 1H), 2.62 (m, 2H), 2.15 (m, 2H), 1.77 (m, 1H), 1.47 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 361 (M+1).

Compound 20: Compound **13** (60 mg, 0.20 mmol), 4-pyridinamine (38 mg, 0.40 mmol), cesium carbonate (100 mg, 0.31 mmol), Xantphos (8 mg, 0.014 mmol), tris(dibenzylideneacetone)dipalladium(0) (4 mg, 0.004 mmol) were weighed in a vial. The vial was sealed, and kept under vacuum. 1,4-dioxane (1 mL, sparged with nitrogen for 10 min) was added. The vial was filled with nitrogen, heated at 100 °C for 16 h, and cooled to room temperature. Acetone was added. The mixture was filtered through a silica gel pad, and eluted with acetone. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% acetone in hexanes) to give compound **20** (70 mg, 97% yield) as a light yellow solid. *m/z* = 353 (M+1).

Compound 21: To a stirred solution of compound **20** (60 mg, 0.17 mmol) in ethyl formate (0.41 mL) was added sodium methoxide (25 wt.% in methanol, 0.58 mL, 2.51 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.42 mL, 2.52 mmol), EtOH (2 mL), and hydroxylamine hydrochloride (18 mg, 0.26 mmol) were added sequentially. The mixture was heated at 55 °C for 2.5 h. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 70% acetone in hexanes) to give compound **21** (52 mg, 81% yield). *m/z* = 378 (M+1).

Compound 22: Compound **21** (45 mg, 0.12 mmol) was dissolved in MeOH (1.2 mL). Sodium methoxide (25 wt.% in methanol, 42 μL, 0.18 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h, and cooled to rt. EtOAc was added. The mixture was washed with aq. 10% NaH_2PO_4. The aqueous wash was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated to give compound **22** as a light brown foamy solid, which was used in the next step without further purification. *m/z* = 378 (M+1).

T8: Compound **22** (all from above) was dissolved in benzene (2.4 mL). DDQ (30 mg, 0.13 mmol) was added. The mixture was heated at 85 °C for 40 min, and was cooled to room temperature. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added, and the mixture was stirred at room temperature for 10 min. The mixture was extracted with CH_2Cl_2. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% acetone in CH_2Cl_2) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 0% to 20% MeOH in CH_2Cl_2) to give compound **T8** (11 mg, 25% yield from compound **21**) as a yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.49 (m, 2H), 7.58

(m, 2H), 7.15 (br s, 1H), 4.04 (s, 3H), 2.77 (ddd, J = 1.2, 7.3, 17.8 Hz, 1H), 2.54 (m, 2H), 2.10 (m, 2H), 1.73 (m, 1H), 1.44 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H); *m/z* = 376.2 (M+1).

Compound 23: To a stirred solution of compound **13** (117 mg, 0.40 mmol) in ethyl formate (0.96 mL) was added sodium methoxide (25 wt.% in methanol, 0.92 mL, 3.98 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.67 mL, 4.02 mmol), EtOH (4 mL), and hydroxylamine hydrochloride (42 mg, 0.60 mmol) were added sequentially. The mixture was heated at 55 °C for 2 h. The solvent was removed. EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% EtOAc in hexanes) to give compound **23** (93 mg, 73% yield). m/z = 320 (M+1).

Compound 25: Compound **23** (50 mg, 0.16 mmol), uinolone-4-boronic acid (45 mg, 0.26 mmol), triphenylphosphine (17 mg, 0.065 mmol), potassium phosphate (108 mg, 0.51 mmol) and palladium acetate (7.6 mg, 0.034 mmol) were weighed in a vial, and kept under vacuum. 1,2-dimethoxyethane (0.7 mL) and DMF (0.35 mL) (sparged with nitrogen for 5 min) were added. The vial was filled with nitrogen, and was heated in Biotage® microwave synthesizer at 110 °C for 5 h. The mixture was cooled to room temperature, filtered through a silica gel plug, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 0% to 10% acetone in CH_2Cl_2) to give a mixture of compound **24** and **25** (15 mg, 23% yield) as a glassy solid. The mixture was dissolved in MeOH (0.72 mL). Sodium methoxide (25 wt.% in methanol, 13 μL, 0.056 mmol) was added. The reaction mixture was stirred at 55 °C for 1.5 h, and cooled to rt. EtOAc was added. The mixture was washed with aq. 10% KH_2PO_4. The organic extract was dried with Na_2SO_4 and concentrated to give compound **25**. *m/z* = 413 (M+1).

T9: Compound **25** (all from above) was dissolved in benzene (0.7 mL). DDQ (9 mg, 0.040 mmol) was added. The mixture was heated at 85 °C for 20 min, and was cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 10% acetone in CH_2Cl_2) to give compound **T9** (6 mg, 40% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 4.8 Hz, 1H), 8.88 (s, 1H), 8.77 (dd, J = 0.8, 8.8 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 4.4 Hz, 1H), 7.77 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.63 (ddd, J = 1.3, 6.8, 8.3 Hz, 1H), 4.12 (s, 3H), 2.95 (dd, J = 6.0, 18.8 Hz, 1H), 2.71 (m, 1H), 2.60 (m, 1H), 2.18 (m, 2H), 1.81 (m, 1H), 1.51 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H); m/z = 411 (M+1).

Compound 26: Compound **13** (100 mg, 0.34 mmol), cesium carbonate (333 mg, 1.02 mmol), potassium *t*-butyl N-[2-(trifluoroboranuidyl)ethyl]carbamate (85 mg, 0.34 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (14 mg, 0.019 mmol) were weighed in a vial. The vial was kept under vacuum. Toluene (3 mL) and water (0.5 mL) (both solvents purged with nitrogen for 5 min) were added. The vial was filled with nitrogen, heated at 100 °C for 16 h, and cooled

to room temperature. The mixture was filtered through a pad of Celite®, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **26** (105 mg, 77% yield). *m/z* = 404 (M+1).

Compound 27 and 28: To a stirred solution of compound **26** (105 mg, 0.26 mmol) in ethyl formate (0.63 mL) was added sodium methoxide (25 wt.% in methanol, 0.90 mL, 3.90 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.65 mL, 3.90 mmol), EtOH (2.6 mL), and hydroxylamine hydrochloride (28 mg, 0.40 mmol) were added sequentially. The mixture was heated at 55 °C for 2 h. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **27** (28 mg, 25% yield) and compound **28** (42 mg, 45% yield) as white foamy solid. Compound **27**: *m/z* = 429 (M+1). Compound **28**: *m/z* = 357 (M+1).

Compound 29: Compound **27** (28 mg, 0.065 mmol) was dissolved in MeOH (0.65 mL). Sodium methoxide (25 wt.% in methanol, 23 μL, 0.10 mmol) was added. The reaction mixture was stirred at 55 °C for 1.5 h, and cooled to rt. EtOAc was added. The mixture was washed with aq. 10% NaH_2PO_4. The aqueous wash was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated to give compound **29**, which was used in the next step without further purification. *m/z* = 429 (M+1).

T10: Compound **29** (all from above) was dissolved in toluene (0.65 mL). DDQ (17 mg, 0.075 mmol) was added. The mixture was heated at 90 °C for 50 min, and was cooled to room temperature. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added, and the mixture was stirred at room temperature for 10 min. The mixture was extracted with CH_2Cl_2. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 15% acetone in hexanes) to give compound **T10** (19 mg, 68% yield from compound **27**) as an off-white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 5.17 (br s, 1H), 3.99 (s, 3H), 3.61 (m, 2H), 3.03 (t, J = 6.5 Hz, 2H), 2.79 (dd, J = 6.7, 18.4 Hz, 1H), 2.54 (m, 2H), 2.09 (m, 2H), 1.71 (m, 1H), 1.44 (s, 9H), 1.39 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); *m/z* = 427 (M+1).

Compound 30: Compound **28** (40 mg, 0.11 mmol) was dissolved in MeOH (1.1 mL). Sodium methoxide (25 wt.% in methanol, 39 μL, 0.17 mmol) was added. The reaction mixture was stirred at 55 °C for 1.5 h, and cooled to rt. EtOAc was added. The mixture was washed with aq. 10% NaH_2PO_4. The aqueous wash was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated to give compound **30**, which was used in the next step without further purification. *m/z* = 357 (M+1).

T11: Compound **30** (all from above) was dissolved in toluene (1.1 mL). DDQ (28 mg, 0.12 mmol) was added. The mixture was heated at 90 °C for 40 min, and was cooled to room temperature. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added, and the mixture was stirred at room temperature for 10 min. The mixture was extracted with CH_2Cl_2. The combined organic extract was dried with Na_2SO_4, and

concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **T11** (20 mg, 50% yield from compound **28**) as an off-white foamy solid. **T11** is 3:1 ratio of formamide tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ [8.80 (s), 8.79 (s), 3:1, 1H], [8.19 (br s), 8.09 (d, J = 12.1 Hz), 3:1, 1H], [6.15 (br s), 6.00 (br s), 3:1, 1H], 3.99 (s, 3H), 3.80 (m, 2H), 3.08 (t, J = 6.4 Hz, 2H), 2.80 (dd, J = 6.7, 18.4 Hz, 1H), 2.55 (m, 2H), 2.09 (m, 2H), 1.71 (m, 1H), 1.39 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); *m/z* = 355 (M+1).

T12: To a solution of compound **T10** (9 mg, 0.021 mmol) in CH_2Cl_2 (0.2 mL) was added TFA (50 μL). The reaction was stirred at room temperature for 1 h, and concentrated. The residue was dissolved in CH_2Cl_2, treated with Et_3N (2 drops), and purified by flash chromatography (silica gel, eluting with 0% to 20% MeOH in CH_2Cl_2) to give compound **T12** (10 mg, quantitative yield) as an off-white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.17 (br s, 2H), 3.95 (s, 3H), 3.49 (m, 2H), 3.22 (t, J = 5.9 Hz, 2H), 2.78 (dd, J = 6.5, 18.4 Hz, 1H), 2.54 (m, 2H), 2.07 (m, 2H), 1.69 (m, 1H), 1.37 (s, 3H), 1.27 (d, J = 6.7 Hz, 3H); *m/z* = 327 (M+1).

Compound 31: To a mixture of 4-amidinopyridine hydrochloride (318 mg, 2.02 mmol) in EtOH (1 mL) was added potassium carbonate (560 mg, 4.06 mmol) and a solution of compound **9** (500 mg, 1.69 mmol) in EtOH (4 mL) sequentially. The reaction was stirred at room temperature for 16 h, and was concentrated. EtOAc (20 mL) and water (2 mL) were added. The mixture was stirred at 65 °C for 10 min, and was cooled to room temperature. Aq. 10% NaH_2PO_4 (10 mL) was added, and the mixture was stirred at room temperature for another 5 min. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% MeOH in CH_2Cl_2) to give compound **31** (400 mg, 65% yield) as a white foamy solid. *m/z* = 368 (M+1).

Compound 32: To a solution of compound **31** (938 mg, 2.56 mmol) in toluene (5 mL) was added phosphorus(V) oxychloride (2.36 mL, 25.6 mmol) at room temperature. The mixture was heated at 100 °C for 1 h, and cooled to room temperature. Aq. sat. $NaHCO_3$ was added slowly to adjust the pH to 7. The mixture was extracted with EtOAc. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% acetone in hexanes) to give compound **32** (618 mg, 71% yield) as an off-white solid. *m/z* = 342 (M+1).

Compound 33: A mixture of compound **32** (618 mg, 1.81 mmol), phenylboronic acid (331 mg, 2.71 mmol), sodium carbonate (575 mg, 5.42 mmol) in 1,4-dioxane (14 mL) and water (5 mL) were sparged with nitrogen for 5 min. [1,1′-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) (265 mg, 0.36 mmol) was added. The mixture was sparged with nitrogen for another 5 min, heated in Biotage® microwave synthesizer at 100 °C for 1 h, and cooled to room temperature. EtOAc and water were added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **33** (640 mg, 92% yield) as a white foamy solid. *m/z* = 384 (M+1).

Compound 34: To a stirred solution of compound **33** (3.01 g, 7.87 mmol) in ethyl formate (19 mL) was added sodium methoxide (25 wt.% in methanol, 27 mL, 116.9 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (20 mL, 120 mmol), EtOH (79 mL), and hydroxylamine hydrochloride (830 mg, 11.9 mmol) were added sequentially. The mixture was heated at 55 °C for 4 h, and was concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **34** (2.62 g, 82% yield) as a white foamy solid. *m/z* = 409 (M+1).

T13: Compound **34** (2.617 g, 6.41 mmol) was dissolved in MeOH (32 mL). Sodium methoxide (25 wt.% in methanol, 2.3 mL, 9.96 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h, and cooled to rt. MTBE and aq. 10% NaH_2PO_4 were added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **T13** (2.363 g, 90% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (m, 2H), 8.34 (m, 2H), 7.60 (m, 2H), 7.51 (m, 3H), 3.92 (dd, J = 5.7, 13.8 Hz, 1H), 3.59 (dd, J = 5.7, 13.7 Hz, 1H), 2.95 (m, 2H), 2.60 (qd, J = 6.5, 12.9 Hz, 1H), 2.28 (t, J = 13.8 Hz, 1H), 2.05 (m, 1H), 1.90 (dt, J = 2.7, 12.4 Hz, 1H), 1.69 (m, 1H), 1.54 (s, 3H), 1.20 (d, J = 6.4 Hz, 3H); *m/z* = 409 (M+1).

T14 and T15: Compound **T13** (2.363 g, 5.79 mmol) was dissolved in anhydrous DMF (14 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (828 mg, 2.90 mmol) in DMF (14 mL) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (1.4 mL, 17.3 mmol) was added. The reaction was heated at 55 °C for 3 h, and cooled to room temperature. EtOAc was added. The mixture was washed with water, aq. 10% Na_2SO_3 and aq. 10% NaH_2PO_4. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene on rotary evaporator. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **T14** (1.515 g, 64% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.80 (m, 2H), 8.37 (m, 2H), 7.60 (m, 2H), 7.53 (m, 3H), 2.99 (m, 2H), 2.62 (m, 1H), 2.27 (dt, J = 2.7, 12.8 Hz, 1H), 2.15 (tdd, J = 2.7, 6.0, 13.8 Hz, 1H), 1.78 (m, 1H), 1.54 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 407 (M+1).

From the column, the fractions containing compound **T15** were combined and concentrated. The crude was purified by flash chromatography (C18, eluting with 0% to 80% MeCN in water) to give compound **T15** (7 mg, 0.3% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (m, 2H), 8.38 (m, 2H), 7.62 (m, 2H), 7.53 (m, 3H), 5.32 (s, 1H), 2.94 (m, 2H), 2.29 (m,, 2H), 1.99 (m, 1H), 1.61 (tdd, J = 6.2, 12.3, 18.6 Hz, 1H), 1.39 (s, 3H), 1.34 (d, J = 7.0 Hz, 3H); *m/z* = 423 (M+1).

T16: A solution of compound **T14** (100 mg, 0.25 mmol) and hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II) (10 mg, 0.023 mmol) in aq. 90% EtOH/water (2.75 mL) was heated at reflux for 16 h. The mixture was concentrated. The residue was purified by flash chromatography (silica gel, 0 to 50 % acetone in CH_2Cl_2) to give compound **T16** (46 mg, 44 % yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.77 (m, 2H), 8.49 (br s,

1H), 8.42 (m, 2H), 7.60 (m, 2H), 7.52 (m, 3H), 5.69 (br s, 1H), 2.96 (m, 2H), 2.64 (m, 1H), 2.24 (dt, J = 2.7, 12.7 Hz, 1H), 2.10 (m, 1H), 1.77 (ddt, J = 7.0, 10.6, 13.4 Hz, 1H), 1.52 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 425 (M+1).

Compound 35: A solution of compound **31** (2.16 g, 5.89 mmol) and aq. 3 N HCl (20 mL, 60 mmol) in MeOH (10 mL) and THF (10 mL) was stirred at room temperature under nitrogen overnight. The sample was concentrated, cooled, basified with aq.10% NH_4OH (50 mL) then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **35** (1.80 g, 95% yield) as light yellow solid, which was used directly in the next step without purification. *m/z* = 324 (M+1).

Compound 36: To a stirring solution at room temperature under nitrogen of compound **35** (1.67 g, 5.16 mmol) and ethyl formate (21 mL, 260 mmol) in THF (25 mL) was added sodium methoxide (30 wt.% solution in methanol, 4.8 mL, 25.6 mmol). After stirring for 16 h, the solution was concentrated then partitioned between aq. sat. KH_2PO_4 (100 mL) and $CHCl_3$ (100 mL). The organic extract was washed with brine (100 mL), dried with $MgSO_4$, filtered and concentrated to give compound **36** (2.09 g) as orange-yellow foamy solid, which was used in the next reaction without purification. *m/z* = 352 (M+1).

Compound 37: A mixture under nitrogen of compound **36** (all from the last step), acetic acid (3 mL, 52.4 mmol) and hydroxylamine hydrochloride (540 mg, 7.77 mmol) in EtOH (25 mL) was heated at 60 °C for 2 h then stirred at room temperature overnight. The solution was concentrated, cooled, carefully basified with aq. sat. $NaHCO_3$ (100 mL) and extracted with $CHCl_3$ (100 mL). The organic extract was washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (silica gel, eluting with 5% MeOH in $CHCl_3$) to give **compound 37** (1.29 g, 72% from compound **35**) as tan foamy solid. *m/z* = 349 (M+1).

Compound 38: To a stirring solution at room temperature under nitrogen of compound **37** (1.29 g, 3.69 mmol) in methanol (37 mL) was added sodium methoxide (30 wt.% solution in methanol, 3.5 mL, 18.7 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (100 mL) and $CHCl_3$ (100 mL). The aqueous phase was back extracted with 20% MeOH in $CHCl_3$ (100 mL). The combined organic extract was dried with $MgSO_4$, filtered and concentrated to give compound **38** (1.03 g, 80% yield) as an off-white solid. *m/z* = 349 (M+1).

T17: To a stirring solution at 0 °C under nitrogen of compound **38** (1.03 g, 2.95 mmol) in DMF (10 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (420 mg, 1.47 mmol) in DMF (3 mL). After stirring at 0 °C for 30 min, pyridine (2.4 mL, 29.7 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and 20% MeOH in $CHCl_3$ (50 mL). The organic extract was dried with $MgSO_4$, filtered and concentrated to give compound **T17** (1.19 g, quantitative yield) as tan foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 13.33 (br s, 1H), 8.87 (m, 2H), 8.80 (s, 1H), 8.18 (m, 2H),

2.92 (m, 1H), 2.62 (m, 2H), 2.20 (m, 1H), 2.12 (dt, J = 2.6, 12.7 Hz, 1H), 1.76 (qdd, J = 6.6, 12.9, 19.5 Hz, 1H), 1.48 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 347 (M+1).

T18: To a stirring solution at room temperature under nitrogen of compound **T17** (1.19 g, ≤ 2.95 mmol), pyridine (0.84 mL, 10.38 mmol) and 4-dimethylaminopyridine (50 mg) in CH_2Cl_2 (30 mL) was added dropwise a solution of *p*-toluenesulfonyl chloride (980 mg, 5.14 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 days, the sample was concentrated then partitioned between aq. sat. KH_2PO_4 (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc then 5% MeOH in EtOAc) to give compound **T18** (341 mg, 23% yield) and recover compound **T17** (507 mg, 49% yield) as tan solid. **T18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.77 (m, 2H), 8.01 (m, 4H), 7.43 (m, 2H), 3.07 (ddd, J = 1.1, 6.8, 18.9 Hz, 1H), 2.84 (ddd, J = 7.6, 11.2, 18.9 Hz, 1H), 2.59 (m, 1H), 2.51 (s, 3H), 2.16 (m, 2H), 1.80 (m, 1H), 1.48 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 501 (M+1).

Compound 39: Compound **8** (2.5 g, 10.5 mmol) was taken up in THF (100 mL). Benzaldehyde (1.15 g, 10.8 mmol) and sodium methoxide (30 wt.% in methanol, 7.5 g, 41.7 mmol) were added. The mixture was stirred overnight at room temperature. The reaction mixture was neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **39** (3.4 g, quantitative yield) as an oil. *m/z* = 327 (M+1).

Compound 40: Compound **39** (3.4 g, 10.4 mmol) was taken up in EtOH (50 mL). Thiourea (6.3 g, 82.8 mmol) and potassium t-butoxide (1.18 g, 10.5 mmol) were added. The reaction mixture was heated at reflux for 16 h, cooled and concentrated. Water (50 mL) was added. The mixture was neutralized with aq. 3 N HCl. The precipitate was collected by filtration, washed with water, and dried under vacuum to give compound **40** (3.8 g, 94% yield) as an off-white solid. *m/z* = 385 (M+1).

Compound 41a: Compound **40** (800 mg, 2.08 mmol) was taken up in 1,4-dioxane (10 mL). Copper(I) thiophene-2-carboxylate (1.2 g, 6.29 mmol), tetrakis(triphenylphosphine)palladium (120 mg, 0.10 mmol) and phenylboronic acid (380 mg, 3.11 mmol) were added. The mixture was bubbled with nitrogen for 10 min, stirred at 100 °C for 16 h, and cooled to room temperature. The reaction mixture was filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% EtOAc in hexanes) to give compound **41a** (250 mg, 28% yield) as an oil. *m/z* = 427 (M+1).

Compound 42a: Compound **41a** (250 mg, 0.59 mmol) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **42a** (220 mg, 98% yield) as a foamy solid. *m/z* = 383 (M+1).

Compound 43a: Compound **42a** (220 mg, 0.57 mmol) was taken up in ethyl formate (15 mL, 186.6 mmol). Sodium methoxide (30 wt.% in MeOH, 420 mg, 2.3 mmol) was added. After the reaction mixture was stirred overnight at room temperature, it was neutralized with aq. KH_2PO_4, and extracted

with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **43a** (240 mg, quantitative yield) as a foamy solid. *m/z* = 411 (M+1).

Compound 44a: Compound **43a** (240 mg, 0.57 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (82 mg, 1.18 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **44a** (220 mg, 92% yield) as a foamy solid. *m/z* = 408 (M+1).

Compound 45a: Compound **44a** (220 mg, 0.54 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in MeOH, 390 mg, 2.2 mmol) was added. After reaction mixture was stirred at room temperature overnight, it was neutralized with aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated to give compound **45a** (220 mg, quantitative yield) as a foamy solid. *m/z* = 408 (M+1).

T19: Compound **45a** (220 mg, 0.54 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (95 mg, 0.59 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction was stirred at 0 °C for 2 h. Pyridine (2 mL, 24.8 mmol) was added. The reaction was allowed to warm to room temperature, and stirred at 50 °C for 16 h. The mixture was concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **T19** (90 mg, 41% yield) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.54 (m, 2H), 7.61 (m, 2H), 7.51 (m, 6H), 2.95 (m, 2H), 2.62 (qd, J = 6.7, 13.3 Hz, 1H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.13 (m, 1H), 1.77 (ddt, J = 7.0, 10.6, 13.3 Hz, 1H), 1.55 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 406 (M+1).

Compound 41b: Compound **40** (800 mg, 2.08 mmol) was taken up in 1,4-dioxane (10 mL). Copper(I) thiophene-2-carboxylate (1.2 g, 6.29 mmol), tetrakis(triphenylphosphine)-palladium (120 mg, 0.10 mmol) and 4-(trifloromethyl)phenylboronic acid (590 mg, 3.11 mmol) were added. The mixture was bubbled with nitrogen for 10 min, stirred at 100 °C for 16 h, and cooled to room temperature. The reaction mixture was filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, 0 to 20% EtOAc in hexanes) to give compound **41b** (290 mg, 28% yield) as a white solid. *m/z* = 495 (M+1).

Compound 42b: Compound **41b** (290 mg, 0.58 mmol) was taken up in THF (4 mL), and aq. 3 N HCl (2 mL, 6.0 mmol) was added. The mixture was stirred overnight at room temperature then concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **42b** (265 mg, quantitative yield) as a foamy solid. *m/z* = 451 (M+1).

Compound 43b: Compound **42b** (265 mg, 0.58 mmol) was taken up in ethyl formate (15 mL, 186.6 mmol). Sodium methoxide (30 wt.% in MeOH, 425 mg, 2.4 mmol) was added. After reaction mixture was stirred at room temperature overnight, it was neutralized with aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **43b** (280 mg, quantitative yield) as a foamy solid. *m/z* = 479 (M+1).

Compound 44b: Compound **43b** (280 mg, 0.58 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (82 mg, 1.18 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, then washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **44b** (270 mg, 97% yield) as a foamy solid. *m/z* = 476 (M+1).

Compound 45b: Compound **44b** (270 mg, 0.57 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in MeOH, 400 mg, 2.2 mmol) was added. After reaction mixture was stirred at room temperature overnight, it was neutralized with aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **45b** (270 mg, quantitative yield) as a foamy solid. *m/z* = 476 (M+1).

T20: Compound **45b** (270 mg, 0.57 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (100 mg, 0.63 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction was stirred at 0 °C for 2 h. Pyridine (2 mL, 24.8 mmol) was added, and the reaction was allowed to warm to room temperature, and stirred at 50 °C for 16 h. The reaction mixture was concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **T20** (105 mg, 39% yield) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.65 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.61 (m, 2H), 7.53 (m, 3H), 2.98 (m, 2H), 2.63 (qd, J = 6.7, 13.3 Hz, 1H), 2.27 (dt, J = 2.6, 12.7 Hz, 1H), 2.15 (m, 1H), 1.79 (m, 1H), 1.55 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H); *m/z* = 474 (M+1).

Compound 46: To a stirring solution at 0 °C under nitrogen of **T17** (1.39 g, 4.01 mmol) and uinolonemine (2.8 mL, 20.1 mmol) in CH_2Cl_2 (80 mL) was added dropwise a solution of trifluoromethanesulfonic anhydride in CH_2Cl_2 (1.0 M, 6 mL, 6.0 mmol). The sample was stirred at 0 °C for 2.5 h, concentrated then partitioned between aq. sat. KH_2PO_4 (100 mL) and EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **46** (905 mg, 47% yield) as a tan solid. *m/z* = 479 (M+1).

T21: In a sealable vial, a mixture of compound **46** (195 mg, 0.408 mmol), 4-(hydroxymethyl)phenylboronic acid (124 mg, 0.82 mmol) and potassium carbonate (170 mg, 1.23 mmol) in 1,4-dioxane (8 mL) was degassed. 1,1'-[bis(diphenylphosphino)-ferrocene]palladium (II) dichloride (30 mg, 0.041 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 48 h. The dark sample was cooled and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 5% MeOH in $CHCl_3$) to give compound **T21** (20 mg, 11% yield) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.80 (m, 2H), 8.37 (m, 2H), 7.62 (m, 2H), 7.54 (m, 2H), 4.82 (s, 2H), 3.00 (m, 2H), 2.63 (qd, J = 6.7, 13.1 Hz, 1H), 2.26 (m, 1H), 2.15 (m, 1H), 1.78 (ddt, J = 7.1, 10.5, 13.3 Hz, 1H), 1.43 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H); *m/z* = 437 (M+1).

Compound 47a: Compound **39** (370 mg, 1.13 mmol) was taken up in EtOH (10 mL). Formamidine acetate (240 mg, 2.30 mmol) and potassium t-butoxide (380 mg, 3.39 mmol) were added. The reaction mixture was heated at reflux for 16 h, cooled and concentrated. The residue was mixed with water (20 mL), and neutralized with aq. 3 N HCl. The precipitate was collected by filtration, washed with water, and dried under vacuum to give compound **47a** (305 mg, 76% yield) as a solid. *m/z* = 353 (M+1).

Compound 48a: Compound **47a** (305 mg, 0.87 mmol) was taken up in CH_2Cl_2 (10 mL). Manganese(IV) oxide (88%, 400 mg, 4.05 mmol) was added. The mixture was stirred overnight at room temperature, and filtered. The filtrate was concentrated to give compound **48a** (260 mg, 86% yield) as a solid. *m/z* = 351 (M+1).

Compound 49a: Compound **48a** (400 mg, 1.14 mmol) was taken up in THF (4 mL), and 3 N HCl (2 mL, 6.0 mmol) was added. The mixture was stirred overnight at room temperature and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give compound **49a** (350 mg, quantitative yield) as a foamy solid. *m/z* = 307 (M+1).

Compound 50a: Compound **49a** (350 mg, 1.14 mmol) was taken up in ethyl formate (15 mL, 186.6 mmol). Sodium methoxide (30 wt.% in methanol, 800 mg, 4.44 mmol) was added. After the mixture was stirred overnight at room temperature, it was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **50a** (380 mg, 99% yield) as a foamy solid. *m/z* = 335 (M+1).

Compound 51a: Compound **50a** (380 mg, 1.14 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (140 mg, 2.01 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **51a** (340 mg, 90% yield) as a foamy solid. *m/z* = 332 (M+1).

Compound 52a: Compound **51a** (340 mg, 1.03 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in MeOH, 800 mg, 4.44 mmol) was added. After the reaction mixture was stirred at room temperature overnight, it was neutralized with aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **52a** (340 mg, quantitative yield) as a foamy solid. *m/z* = 332 (M+1).

T22: Compound **52a** (340 mg, 1.03 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (180 mg, 1.13 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 24.8 mmol) was added. The reaction was allowed to warm to room temperature, and stirred at 50 °C for 16 h. The reaction mixture was concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T22** (150 mg, 44% yield) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.91 (s, 1H), 7.49 (m, 5H), 2.93 (m, 2H), 2.59 (qd, J = 6.7, 13.4 Hz, 1H), 2.21 (dt, J = 2.7, 12.8 Hz, 1H), 2.10 (m, 1H), 1.74 (m, 1H), 1.48 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); *m/z* = 330 (M+1).

Compound 47b: Compound **39** (780 mg, 2.39 mmol) was taken up in EtOH (10 mL). Cyclohexanecarboximidamide HCl salt (650 mg, 4.00 mmol) and potassium *t*-butoxide (560 mg, 4.99 mmol) were added. The reaction mixture was heated at reflux for 16 h, cooled and concentrated. The residue was mixed with water (20 mL), neutralized with aq. 3 N HCl, and extracted with EtOAc. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **47b** (1.05 g, quantitative yield) as an oil. *m/z* = 435 (M+1).

Compound 48b: Compound **47b** (1.05 g, 2.42 mmol) was taken up in CH_2Cl_2 (20 mL). Manganese(IV) oxide (88%, 600 mg, 6.07 mmol) was added. The mixture was stirred for 3 days at room temperature, and filtered. The filtrate was concentrated to give compound **48b** (900 mg, 86% yield) as a solid. *m/z* = 433 (M+1).

Compound 49b: Compound **48b** (900 mg, 2.08 mmol) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give compound **49b** (700 mg, 86% yield) as a foamy solid. *m/z* = 389 (M+1).

Compound 50b: Compound **49b** (700 mg, 1.8 mmol) was taken up in ethyl formate (15 mL, 187.5 mmol). Sodium methoxide (30 wt.% in methanol, 1300 mg, 7.2 mmol) was added. The mixture was stirred overnight at room temperature. The reaction mixture was neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give a foam compound **50b** (745 mg, quantitative yield). *m/z* = 417 (M+1).

Compound 51b: Compound **50b** (745 mg, 1.80 mmol) was dissolved in EtOH (20 mL). Hydroxylamine hydrochloride (245 mg, 3.52 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **51b** (650 mg, 88% yield) as a foamy solid. *m/z* = 414 (M+1).

Compound 52b: Compound **51b** (650 mg, 1.57 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in MeOH, 1100 mg, 6.11 mmol) was added. After the reaction mixture was stirred at room temperature overnight, it was neutralized with aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **52b** (350 mg, 54% yield) as a foamy solid. *m/z* = 414 (M+1).

T23: Compound **52b** (350 mg, 0.84 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (150 mg, 0.94 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added. The reaction was allowed to warm to room temperature, and stirred at 50 °C for 16 h. The reaction mixture was concentrated. The crude residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **T23** (150 mg, 43% yield) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.47

(m, 5H), 2.88 (m, 3H), 2.58 (qd, J = 6.7, 13.4 Hz, 1H), 2.19 (dt, J = 2.7, 12.8 Hz, 1H), 2.05 (m, 3H), 1.87 (m, 2H), 1.73 (m, 4H), 1.46 (s, 3H), 1.39 (m, 3H), 1.29 (d, J = 6.7 Hz, 3H); m/z = 412 (M+1).

Compound 53: To a stirring solution at 0 °C under nitrogen of compound **31** (1.00 g, 2.72 mmol) and uinolonemine (1.9 mL, 13.6 mmol) in CH_2Cl_2 (27 mL) was added dropwise a solution of trifluoromethanesulfonic anhydride in CH_2Cl_2 (1.0 M, 4 mL, 4.0 mmol). The sample was stirred at 0 °C for 45 min, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (100 mL) and EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **53** (322 mg, 24% yield) as a tan solid. *m/z* = 500 (M+1).

Compound 54: In a sealable vial, a mixture of compound **53** (257 mg, 0.514 mmol), 4-(trifluoromethyl)phenylboronic acid (147 mg, 0.774 mmol) and potassium phosphate (330 mg, 1.55 mmol) in DME (10 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.051 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 16 h. The dark sample was cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **54** (106 mg, 41% yield) as a tan foamy solid. *m/z* = 496 (M+1).

Compound 55: A solution of compound **54** (106 mg, 0.214 mmol) and aq. 3 N HCl (0.7 mL, 2.1 mmol) in MeOH (20 mL) was stirred at room temperature under nitrogen overnight. The sample was concentrated, cooled, basified with aq. 10% NH_4OH (25 mL) then extracted with $CHCl_3$ (2 × 25 mL). The combined organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated to give compound **55** (95 mg, 98% yield) as a tan foamy solid, which was used directly in the next step without purification. *m/z* = 452 (M+1).

Compound 56: To a stirring solution at room temperature under nitrogen of compound **55** (95 mg, 0.21 mmol) in ethyl formate (2.0 mL, 24.8 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.20 mL, 1.07 mmol). After 16 h, the solution was concentrated, and then partitioned between aq. sat. KH_2PO_4 (10 mL) and $CHCl_3$ (10 mL). The organic extract was washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated to give compound **56** (112 mg) as a yellow oil, which was used in the next reaction without purification. *m/z* = 480 (M+1).

Compound 57: A mixture under nitrogen of compound **56** (all from the last step), and hydroxylamine hydrochloride (37 mg, 0.53 mmol) in EtOH (2 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, carefully basified with aq. sat. $NaHCO_3$ (25 mL) and extracted with $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated to give compound **57** (98 mg, 98% yield from compound **55**) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 477 (M+1).

Compound 58: To a stirring solution at room temperature under nitrogen of compound **57** (98 mg, 0.206 mmol) in MeOH (5 mL) was added sodium methoxide (30 wt.% solution in methanol, 0.20

mL, 1.10 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **58** (46 mg, 47% yield) as a yellow oil. *m/z* = 477 (M+1).

T24: To a stirring solution at 0 °C under nitrogen of compound **58** (42 mg, 0.088 mmol) in DMF (3 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (13 mg, 0.045 mmol) in DMF (1 mL). After the mixture was stirred at 0 °C for 30 min, pyridine (0.10 mL, 1.24 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T24** (14 mg, 33% yield) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.81 (d, J = 5.2 Hz, 2H), 8.35 (m, 2H), 7.80 (d, J = 7.7 Hz, 2H), 7.73 (d, J = 7.7 Hz, 2H), 2.96 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.27 (dt, J = 2.7, 12.8 Hz, 1H), 2.17 (m, 1H), 1.80 (m, 1H), 1.56 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 60: In a sealable vial, a suspension of compound **31** (1.31 g, 3.56 mmol) and phosphorus(V) oxychloride (3.3 mL, 35.4 mmol) in toluene (7 mL) was flushed with nitrogen. The vial was sealed and heated at 100 °C for 1 h. The solution was cooled and slowly poured into a stirring suspension of $NaHCO_3$ (15 g, 178 mmol) in water (100 mL). The sample was stirred at room temperature for 20 min, and then extracted with EtOAc (2 × 100 mL). The organic extract was washed with brine (200 mL), dried with $MgSO_4$, filtered, concentrated. The residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give a mixture of compound **59** and **60** (714 mg) as off-white solid. *m/z* = 386 (**59**, M+1) and 342 (**60**, M+1).

A solution of the above mixture of compound **59** and **60** (714 mg) and aq. 3 N HCl (5.5 mL, 16.5 mmol) in MeOH (10 mL) and THF (10 mL) was stirred at room temperature under nitrogen overnight. The sample was concentrated, cooled, basified with aq. 10% NH_4OH to pH ~9-10, and then extracted with $CHCl_3$ (2 × 50 mL). The combined organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **60** (616 mg, 50% yield from compound **31**) as a light yellow solid. *m/z* = 342 (M+1).

Compound 61a: In a sealable vial, a mixture of compound **60** (243 mg, 0.711 mmol), 3-pyridinylboronic acid (130 mg, 1.06 mmol) and potassium phosphate (450 mg, 2.12 mmol) in 1,4-dioxane (7 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (82 mg, 0.071 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 48 h. The dark sample was cooled, concentrated, and then partitioned between aq. sat. KH_2PO_4 (25 mL) and $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 5% MeOH in EtOAc) to give compound **61a** (257 mg, 94% yield) as a dark yellow oil. *m/z* = 385 (M+1).

Compound 62a: To a stirring solution at room temperature under nitrogen of compound **61a** (257 mg, 0.668 mmol) in ethyl formate (4.5 mL, 55.9 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.63 mL, 3.36 mmol). After 16 h, the solution was concentrated, and then partitioned between aq. sat. KH_2PO_4 (25 mL) and $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated to give compound **62a** (276 mg, quantitative yield) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 413 (M+1).

Compound 63a: A mixture under nitrogen of compound **62a** (276 mg, 0.668 mmol) and hydroxylamine hydrochloride (230 mg, 3.31 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, and carefully basified with aq. sat. $NaHCO_3$ (100 mL). The mixture was extracted with $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by column and chromatography (silica gel, eluting with 100% EtOAc) to give compound **63a** (134 mg, 49% yield) as an off-white solid. *m/z* = 410 (M+1).

Compound 64a: To a stirring solution at room temperature under nitrogen of compound **63a** (134 mg, 0.327 mmol) in methanol (5 mL) and THF (5 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.31 mL, 1.65 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated to give compound **64a** (198 mg) as a yellow oil, which was used in the next reaction without purification. *m/z* = 410 (M+1).

T25: To a stirring solution at 0 °C under nitrogen of compound **64a** (all from the last step) in DMF (7 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (47 mg, 0.164 mmol) in DMF (3 mL). After stirring at 0 °C for 30 min, pyridine (0.26 mL, 3.21 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 5% MeOH in $CHCl_3$) to give compound **T25** (68 mg, 51% yield from compound **63a**) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.90 (dd, J = 0.9, 2.3 Hz, 1H), 8.82 (m, 2H), 8.77 (dd, J = 1.7, 4.9 Hz, 1H), 8.36 (m, 2H), 7.98 (ddd, J = 1.7, 2.3, 7.9 Hz, 1H), 7.49 (ddd, J = 0.9, 4.9, 7.9 Hz, 1H), 3.02 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.28 (dt, J = 2.7, 12.7 Hz, 1H), 2.18 (ddd, J = 2.8, 6.1, 12.0 Hz, 1H), 1.82 (ddt, J = 7.0, 10.3, 13.5 Hz, 1H), 1.56 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 408 (M+1).

Compound 61b: In a sealable vial, a mixture of compound **60** (327 mg, 0.956 mmol), 3-(trifluoromethyl)phenylboronic acid (360 mg, 1.90 mmol) and potassium phosphate (610 mg, 2.87 mmol) in DME (6 mL) and DMF (3 mL) was degassed. Tetrakis(triphenylphosphine)-palladium(0) (110 mg, 0.095 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 48 h. The dark sample was cooled, concentrated, and then partitioned between aq. sat. KH_2PO_4 (25 mL) and $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$,

filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes) to give compound **61b** (556 mg) as a dark yellow oil. *m/z* = 452 (M+1).

Compound 62b: To a stirring solution at room temperature under nitrogen of compound **61b** (all from the last step) in ethyl formate (10 mL, 123 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.90 mL, 4.80 mmol). After 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated to give compound **62b** (567 mg) as a yellow-orange foamy solid, which was used in the next reaction without purification. *m/z* = 480 (M+1).

Compound 63b: A mixture under nitrogen of compound **62b** (all from the last step) and hydroxylamine hydrochloride (170 mg, 2.45 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, carefully basified with aq. sat. $NaHCO_3$ (25 mL). The mixture was extracted with $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated to give compound **63b** (512 mg) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 477 (M+1).

Compound 64b: To a stirring solution at room temperature under nitrogen of compound **63b** (all from the last step) in MeOH (25 mL) was added sodium methoxide (30 wt.% solution in methanol, 0.90 mL, 4.80 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered and concentrated to give compound **64b** (468 mg) as a yellow-orange foamy solid, which was used in the next reaction without purification. *m/z* = 477 (M+1).

T26: To a stirring solution at 0 °C under nitrogen of compound **64b** (all from the last step) in DMF (6 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (137 mg, 0.479 mmol) in DMF (3 mL). After stirring at 0 °C for 30 min, pyridine (0.77 mL, 9.52 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T26** (26 mg, 6% yield from compound **60**) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.81 (m, 2H), 8.36 (m, 2H), 7.87 (m, 1H), 7.80 (m, 2H), 7.68 (t, J = 7.8 Hz, 1H), 2.95 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.28 (dt, J = 2.8, 12.8 Hz, 1H), 2.18 (m, 1H), 1.80 (ddt, J = 6.8, 10.8, 13.4 Hz, 1H), 1.55 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 61c: In a sealable vial, a mixture of compound **60** (200 mg, 0.585 mmol), 4-methylphenylboronic acid (160 mg, 1.17 mmol) and potassium phosphate (370 mg, 1.74 mmol) in 1,4-dioxane (6 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (68 mg, 0.059 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 16 h. The dark sample was cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and

concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **61c** (273 mg) as a light yellow oil. *m/z* = 398 (M+1).

Compound 62c: To a stirring solution at room temperature under nitrogen of compound **61c** (all from the last step) in ethyl formate (10 mL, 123 mmol) was added sodium methoxide (30 wt.% solution in methanol, 0.65 mL, 3.46 mmol). After 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **62c** (269 mg) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 426 (M+1).

Compound 63c: A mixture under nitrogen of compound **62c** (all from the last step) and hydroxylamine hydrochloride (100 mg, 1.44 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, and carefully basified with sat. $NaHCO_3$ (50 mL). The mixture was extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **63c** (257 mg) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 423 (M+1).

Compound 64c: To a stirring solution at room temperature under nitrogen of compound **63c** (all from the last step) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.57 mL, 3.04 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **64c** (209 mg, 84% yield from compound **60**) as tan foamy solid, which was used in the next reaction without purification. *m/z* = 423 (M+1).

T27: To a stirring solution at 0 °C under nitrogen of compound **64c** (209 mg, 0.495 mmol) in DMF (6 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (71 mg, 0.248 mmol) in DMF (3 mL). After stirring at 0 °C for 30 min, pyridine (0.40 mL, 4.96 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T27** (84 mg, 40% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.79 (m, 2H), 8.37 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 3.00 (m, 2H), 2.62 (qd, J = 6.7, 13.4 Hz, 1H), 2.46 (s, 3H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.15 (ddd, J = 3.2, 6.3, 14.0 Hz, 1H), 1.77 (ddt, J = 7.3, 10.3, 13.3 Hz, 1H), 1.54 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 421 (M+1).

Compound 61d: In a sealable vial, a mixture of compound **60** (200 mg, 0.585 mmol), 4-chlorophenylboronic acid (180 mg, 1.15 mmol) and potassium phosphate (370 mg, 1.74 mmol) in 1,4-dioxane (6 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (68 mg, 0.059 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 16 h. The dark sample was cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and

concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **61d** (224 mg, 92% yield) as a tan foamy solid. *m/z* = 418 (M+1).

Compound 62d: To a stirring solution at room temperature under nitrogen of compound **61d** (224 mg, 0.536 mmol) in ethyl formate (10 mL, 123 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.50 mL, 2.66 mmol). After 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **62d** (288 mg) as yellow oil, which was used in the next reaction without purification. *m/z* = 446 (M+1).

Compound 63d: A mixture under nitrogen of compound **62d** (all from the last step) and hydroxylamine hydrochloride (100 mg, 1.44 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, and carefully basified with aq. sat. $NaHCO_3$ (50 mL). The mixture was extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **63d** (235 mg, 99% yield from compound **61d**) as a light yellow foamy solid, which was used in the next reaction without purification. *m/z* = 443 (M+1).

Compound 64d: To a stirring solution at room temperature under nitrogen of compound **63d** (235 mg, 0.530 mmol) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.50 mL, 2.66 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes) to give compound **64d** (130 mg, 55% yield) as a light yellow solid. *m/z* = 443 (M+1).

T28: To a stirring solution at 0 °C under nitrogen of compound **64d** (130 mg, 0.293 mmol) in DMF (6 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (42 mg, 0.146 mmol) in DMF (3 mL). After stirring the mixture at 0 °C for 30 min, pyridine (0.25 mL, 3.09 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes), and then washed with Et_2O to give compound **T28** (40 mg, 31% yield) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.81 (m, 2H), 8.35 (m, 2H), 7.57 (m, 2H), 7.51 (m, 2H), 2.99 (m, 2H), 2.63 (qd, J = 6.7, 13.4 Hz, 1H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.16 (tdd, J = 2.7, 6.0, 14.0 Hz, 1H), 1.79 (ddt, J = 7.1, 10.4, 13.3 Hz, 1H), 1.54 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 441 (M+1).

Compound 61e: In a sealable vial, a mixture of compound **60** (200 mg, 0.585 mmol), 4-pyridinylboronic acid (140 mg, 1.14 mmol) and potassium phosphate (370 mg, 1.74 mmol) in 1,4-dioxane (6 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (68 mg, 0.059 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 16 h. The dark sample was cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25

mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 5% MeOH in EtOAc) to give compound **61e** (90 mg, 40% yield) as a white foamy solid. *m/z* = 385 (M+1).

Compound 62e: To a stirring solution at room temperature under nitrogen of compound **61e** (90 mg, 0.234 mmol) in ethyl formate (10 mL, 123 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.22 mL, 1.17 mmol). After 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **62e** (102 mg) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 413 (M+1).

Compound 63e: A mixture under nitrogen of compound **62e** (all from the last step) and hydroxylamine hydrochloride (41 mg, 0.59 mmol) in EtOH (25 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, and carefully basified with aq. sat. $NaHCO_3$ (50 mL). The mixture was extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **63e** (72 mg, 75% yield from compound **61e**) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 410 (M+1).

Compound 64e: To a stirring solution at room temperature under nitrogen of compound **63e** (72 mg, 0.176 mmol) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.17 mL, 0.91 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **64e** (58 mg, 80% yield) as a tan foamy solid. *m/z* = 410 (M+1).

T29: To a stirring solution at 0 °C under nitrogen of compound **64e** (58 mg, 0.142 mmol) in DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (20 mg, 0.070 mmol) in DMF (1 mL). After stirring the mixture at 0 °C for 30 min, pyridine (0.11 mL, 1.36 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 5% MeOH in $CHCl_3$) to give compound **T29** (13 mg, 22% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.82 (m, 4H), 8.35 (m, 2H), 7.51 (m, 2H), 2.97 (m, 2H), 2.64 (qd, J = 6.8, 13.4 Hz, 1H), 2.27 (dt, J = 2.7, 12.8 Hz, 1H), 2.19 (m, 1H), 1.82 (m, 1H), 1.55 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H); *m/z* = 408 (M+1).

Compound 61f: In a sealable vial, a mixture of compound **60** (200 mg, 0.585 mmol), 4-methoxyphenylboronic acid (180 mg, 1.18 mmol) and potassium phosphate (370 mg, 1.74 mmol) in 1,4-dioxane (6 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (68 mg, 0.059 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 16 h. The dark sample was cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and

concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% to 75% EtOAc in hexanes) to give compound **61f** (249 mg) as a light yellow oil. *m/z* = 414 (M+1).

Compound 62f: To a stirring solution at room temperature under nitrogen of compound **61f** (all from the last step) in ethyl formate (10 mL, 123 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.56 mL, 2.98 mmol). After 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **62f** (253 mg, 98% yield from compound **60**) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 442 (M+1).

Compound 63f: A mixture under nitrogen of compound **62f** (253 mg, 0.573 mmol) and hydroxylamine hydrochloride (100 mg, 1.44 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, and carefully basified with aq. sat. $NaHCO_3$ (50 mL). The mixture was extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **63f** (268 mg) as tan foamy solid, which was used in the next reaction without purification. *m/z* = 439 (M+1).

Compound 64f: To a stirring solution at room temperature under nitrogen of compound **63f** (all from the last step) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in methanol, 0.57 mL, 3.04 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **64f** (158 mg, 62% yield from compound **62f**) as light a yellow oil. *m/z* = 439 (M+1).

T30: To a stirring solution at 0 °C under nitrogen of compound **64f** (158 mg, 0.360 mmol) in DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (52 mg, 0.182 mmol) in DMF (1 mL). After stirring the mixture at 0 °C for 30 min, pyridine (0.30 mL, 3.71 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T30** (54 mg, 34% yield) as a light yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.80 (m, 2H), 8.37 (m, 2H), 7.63 (m, 2H), 7.04 (m, 2H), 3.90 (s, 3H), 3.04 (m, 2H), 2.63 (qd, J = 6.7, 13.3 Hz, 1H), 2.27 (dt, J = 2.7, 12.8 Hz, 1H), 2.16 (m, 1H), 1.79 (m, 1H), 1.53 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H); *m/z* = 437 (M+1).

Compound 61g: In a sealable vial, a mixture of compound **60** (200 mg, 0.585 mmol), 3,4-dichlorophenylboronic acid (130 mg, 0.68 mmol) and potassium phosphate (370 mg, 1.74 mmol) in 1,4-dioxane (6 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (68 mg, 0.059 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 16 h. The dark sample was cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and

EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **61g** (206 mg, 78% yield) as a white foamy solid. *m/z* = 452 (M+1).

Compound 62g: To a stirring solution at room temperature under nitrogen of compound **61g** (206 mg, 0.455 mmol) in ethyl formate (10 mL, 123 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.43 mL, 2.29 mmol). After 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **62g** (234 mg) as yellow oil, which was used in the next reaction without purification. *m/z* = 480 (M+1).

Compound 63g: A mixture under nitrogen of compound **62g** (all from the last step) and hydroxylamine hydrochloride (85 mg, 1.22 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, and carefully basified with aq. sat. $NaHCO_3$ (50 mL). The mixture was extracted with EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give compound **63g** (200 mg, 92% yield from compound **61g**) as a light yellow foamy solid, which was used in the next reaction without purification. *m/z* = 477 (M+1).

Compound 64g: To a stirring solution at room temperature under nitrogen of compound **63g** (200 mg, 0.419 mmol) in MeOH (10 mL) and THF (10 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.39 mL, 2.08 mmol). The sample was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **64g** (128 mg, 64% yield) as a light yellow foamy solid. *m/z* = 477 (M+1).

T31: To a stirring solution at 0 °C under nitrogen of compound **64g** (128 mg, 0.268 mmol) in DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (38 mg, 0.133 mmol) in DMF (1 mL). After stirring the mixture at 0 °C for 30 min, pyridine (0.22 mL, 2.72 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T31** (74 mg, 58% yield) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.82 (m, 2H), 8.35 (m, 2H), 7.72 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.46 (dd, J = 2.1, 8.3 Hz, 1H), 2.97 (m, 2H), 2.63 (qd, J = 6.7, 13.3 Hz, 1H), 2.23 (m, 2H), 1.80 (ddt, J = 7.2, 10.4, 13.3 Hz, 1H), 1.54 (s, 3H), 1.34 (d, J – 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 65 and 66: Compound **12** (1120 mg, 3.75 mmol) was taken up in 1,4-dioxane (20 mL). Potassium carbonate (770 mg, 5.58 mmol), [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (270 mg, 0.37 mmol) and phenylboronic acid (456 mg, 3.73 mmol) were added. After sparged with nitrogen for 10 min, the mixture was heated at 90 °C for 16 h, cooled, and

filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **65** (830 mg, 65% yield) and compound **66** (220 mg, 17% yield) as foamy solid. Compound **65**: *m/z* = 341 (M+1). Compound **66**: *m/z* = 341 (M+1).

Compound 67: Compound **65** (830 mg, 2.43 mmol) was taken up in 1,4-dioxane/DMF (3:1, 10 mL). Potassium carbonate (550 mg, 3.99 mmol), [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (190 mg, 0.26 mmol) and quinolin-4-ylboronic acid (450 mg, 2.60 mmol) were added. After sparged with nitrogen for 10 min, the mixture was heated at 100 °C for 16 h, cooled, and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, 0 to 30% EtOAc in hexanes) to give compound **67** (160 mg, 15% yield) as a foamy solid. *m/z* = 434 (M+1).

Compound 68: To a stirring mixture of compound **67** (160 mg, 0.37 mmol) in ethyl formate (15 mL, 186.5 mmol) was added sodium methoxide (30 wt.% in MeOH, 300 mg, 1.67 mmol) at room temperature. After overnight stirring, the mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **68** (170 mg, quantitative yield) as a foamy solid. *m/z* = 462 (M+1).

Compound 69: Compound **68** (170 mg, 0.37 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (55 mg, 0.79 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **69** (165 mg, 98% yield) as a foamy solid. *m/z* = 459 (M+1).

Compound 70: Compound **69** (165 mg, 0.36 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in MeOH, 300 mg, 1.67 mmol) was added at room temperature. After stirring overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated to give compound **70** (165 mg, quantitative yield) as a foamy solid. *m/z* = 459 (M+1).

T32: Compound **70** (165 mg, 0.36 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (62 mg, 0.39 mmol) in CH_2Cl_2 (1 ml) was added, and the reaction was stirred at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added. The reaction was allowed to warm to room temperature, and heated at 50 °C for 16 h. The mixture was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **T32** (45 mg, 27% yield) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.4 Hz, 1H), 8.95 (s, 1H), 8.74 (dd, J = 1.4, 8.7 Hz, 1H), 8.22 (dd, J = 0.8, 8.8 Hz, 1H), 8.03 (d, J = 4.4 Hz, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.63 (m, 3H), 7.53 (m, 3H), 3.05 (m, 2H), 2.64 (td, J = 6.7, 13.4 Hz, 1H), 2.32 (dt, J = 2.7, 12.8 Hz, 1H), 2.19 (tdd, J = 2.9, 6.1, 12.2 Hz, 1H), 1.84 (m, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); m/z = 457 (M+1).

Compound 71: Compound **65** (450 mg, 1.32 mmol) was taken up in 1,4-dioxane/DMF (3:1, 10 mL). Potassium carbonate (550 mg, 3.99 mmol), [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (100 mg, 0.14 mmol) and 2-methoxypyridine-4-boronic acid (400 mg,

2.62 mmol) were added. After sparged with nitrogen for 10 min, the mixture was heated at 100 °C for 16 h, cooled, and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, 0 to 50% EtOAc in hexanes) to give compound **71** (510 mg, 93% yield) as a foamy solid. *m/z* = 414 (M+1).

Compound 72: To a stirring mixture of compound **71** (510 mg, 1.23 mmol) in ethyl formate (15 mL, 186.5 mmol) was added sodium methoxide (30 wt.% in MeOH, 900 mg, 5.00 mmol) at room temperature. After overnight stirring, the mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **72** (545 mg, quantitative yield) as a foamy solid. *m/z* = 442 (M+1).

Compound 73: Compound **72** (545 mg, 1.23 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (175 mg, 2.52 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **73** (540 mg, 99% yield) as a foamy solid. *m/z* = 439 (M+1).

Compound 74: Compound **73** (540 mg, 1.23 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in MeOH, 900 mg, 5.00 mmol) was added at room temperature. After stirring overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated to give compound **74** (410 mg, 76% yield) as a foamy solid. *m/z* = 439 (M+1).

T33: Compound **74** (410 mg, 0.93 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (165 mg, 1.03 mmol) in CH_2Cl_2 (1 ml) was added, and the reaction was stirred at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added. The reaction was allowed to warm to room temperature, and heated at 50 °C for 16 h. The mixture was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **T33** (150 mg, 37% yield) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.33 (dd, J = 0.7, 5.4 Hz, 1H), 7.95 (dd, J = 1.4, 5.4 Hz, 1H), 7.85 (dd, J = 0.7, 1.5 Hz, 1H), 7.60 (m, 2H), 7.52 (m, 3H), 4.02 (s, 3H), 2.99 (m, 2H), 2.62 (qd, J = 6.7, 13.3 Hz, 1H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.14 (tdd, J = 2.7, 6.2, 13.9 Hz, 1H), 1.77 (ddt, J = 7.0, 10.6, 13.4 Hz, 1H), 1.53 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 437 (M+1).

Compound 75: Compound **8** (5.04 g, 21.2 mmol) was taken up in CH_2Cl_2 (200 mL) and magnesium bromide diethyletherate (13.08 g, 50.6 mmol) was added followed by and *N,N*-diisopropylethylamine (10.8 mL, 62.0 mmol) at room temperature. The mixture was stirred for 30 min, and benzoyl chloride (3.3 mL, 28.4 mmol) was added. The mixture was stirred overnight at room temperature, and then washed with aq. sat. KH_2PO_4 (100 mL), aq. sat. $NaHCO_3$ (100 mL), and brine. The organic extract was dried over $MgSO_4$, concentrated, and dried under vacuum. The crude product was triturated with hexanes, and the solid was collected by filtration and dried to give of compound **75** (6.91 g, 95% yield) as a tan solid. *m/z* = 343 (M+1).

Compound 76: Compound **75** (1.907 g, 5.57 mmol) and guanidine carbonate (1.20 g, 13.32 mmol) were mixed in EtOH (50 mL), and sodium methoxide (5.4 M solution in MeOH, 2.2 mL, 11.88 mmol) was added. The mixture was heated at reflux overnight, then cooled and concentrated. The residue was partitioned between EtOAc (200 mL) and aq. sat. $NaHCO_3$ (100 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 40% EtOAc in hexanes) to give compound **76** (744 mg, 37% yield) as a light yellow foam. *m/z* = 366 (M+1).

Compound 77: Compound **76** (681 mg, 1.86 mmol) was taken up in MeOH (20 mL) and aq. 1 N HCl (6 mL) was added. The solution was stirred overnight and then concentrated. The residue was partitioned between EtOAc (200 mL) and aq. sat. $NaHCO_3$. The organic extract was washed with brine (30 mL), dried over $MgSO_4$, and concentrated to give compound **77** as a clear glass, which was used directly in the next step. *m/z* = 322 (M+1).

Compound 78 and 79: Compound **77** (all from the last step) was taken up in ethyl formate (20 mL) and sodium methoxide (5.4 M solution in MeOH, 1 mL, 5.4 mmol) was added. The solution was stirred overnight at room temperature, and then partitioned between EtOAc (150 mL) and aq. sat. KH_2PO_4 (40 mL). The organic extract was dried over $MgSO_4$ and concentrated to give a mixture of compound **78** and compound **79** (0.63 g) as a waxy glass. *m/z* = 350 (M+1, compound **78**), 378 (M+1, compound **79**).

Compound 80: Compound **78** and compound **79** (0.62 g) were mixed with hydroxylamine hydrochloride (0.376 g, 5.41 mmol) in EtOH (40 mL) and water (2 mL). The mixture was stirred at room temperature overnight, and concentrated. The residue was partitioned between EtOAc (200 mL) and aq. sat. $NaHCO_3$ (50 mL). The organic layer was separated, washed with brine (30 mL), dried over $MgSO_4$, and concentrated to give compound **80** (0.485 g, 75% yield from compound **76**) as a foam. *m/z* = 347 (M+1).

Compound 81: Compound **80** (0.485 g, 1.40 mmol) was mixed in THF (30 mL) and MeOH (1 mL). Sodium methoxide (5.4 M solution in MeOH, 1 mL, 5.4 mmol) was added. The solution was stirred overnight at room temperature, and then partitioned between EtOAc (200 mL) and aq. sat. KH_2PO_4 (100 mL). The organic layer was separated, dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **81** (0.498 g, quantitative yield).

T34: Compound **81** (0.49 g, 1.41 mmol) was taken up in DMF (4 mL) and cooled in an ice bath. 1,3-dibromo-5,5-dimethylhydantoin (0.227 g, 0.79 mmol) was added and the solution was stirred 1 h at 0 °C. Pyridine (1 mL, 12.4 mmol) was added and the solution was heated at 65 °C for 3 h and then concentrated. The residue was partitioned between EtOAc (200 mL) and aq. sat. KH_2PO_4 (50 mL). The organic layer was washed with aq. sat. $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give impure **T34** (152 mg), which was purified again by flash chromatography (silica gel, eluting with 10% EtOAc in CH_2Cl_2) to give compound **T34** (18.8 mg, 4% yield) as a yellow foam. ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.46 (m, 5H), 4.99 (br s, 2H), 2.70 (m, 2H), 2.53 (td, J = 6.7,

13.4 Hz, 1H), 2.14 (dt, J = 2.7, 12.8 Hz, 1H), 2.02 (m, 1H), 1.67 (m, 1H), 1.44 (s, 3H), 1.28 (d, J = 6.7 Hz, 3H); *m/z* = 345 (M+1).

T35: A mixture of **T34** (48 mg, 0.14 mmol), pyridine (0.1 mL, 1.24 mmol), and cyclohexanecarbonyl chloride (48 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature overnight. The mixture was concentrated and EtOAc was added. The insoluble material was filtered off, and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 5% EtOAc in CH_2Cl_2) to give impure **T35**, which was taken up in EtOAc, and washed with aq. sat. $NaHCO_3$ and brine. The organic extract was dried over $MgSO_4$, filtered and concentrated. The residue was purified twice by flash chromatography (silica gel, eluting with 5% EtOAc in CH_2Cl_2) to give compound **T35** (14.8 mg, 23% yield) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.92 (br s, 1H), 7.49 (m, 5H), 2.86 (m, 2H), 2.56 (td, J = 6.7, 13.3 Hz, 1H), 2.19 (dt, J = 2.7, 12.8 Hz, 1H), 2.13-1.25 (m, 13H), 1.49 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); *m/z* = 455 (M+1).

Compound 82: To a stirring solution at room temperature under nitrogen of compound **8** (2.50 g, 10.49 mmol) and *N,N*-diisopropylethylamine (5.5 mL, 31.6 mmol) in CH_2Cl_2 (52 mL) was added in one portion magnesium bromide diethyl etherate (6.8 g, 26.3 mmol). The suspension was stirred for 30 min, then a solution of phenylacetyl chloride (1.5 mL, 11.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The sample was stirred at room temperature under nitrogen overnight, and concentrated. The residue was mixed with aq. sat. KH_2PO_4 (100 mL) and EtOAc (100 mL), and filtered through a pad of Celite® to remove insoluble material. The layers of the filtrate were separated. The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give crude compound **82** (4.15 g, quantitative yield), which was used directly in the next step without purification. *m/z* = 357 (M+1).

Compound 83: A mixture of compound **82** (2.08 g, assuming 5.25 mmol), 4-amidinopyridine hydrochloride (1.00 g, 6.34 mmol) and potassium carbonate (1.74 g, 12.59 mmol) in EtOH (5 mL) was stirred at room temperature under nitrogen for 5 days. The sample was concentrated, and the residue was partitioned between aq. sat. KH_2PO_4 (100 mL) and EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give impure compound **83** (1.92 g, 83% yield from compound **8**) as a yellow oil, which was used directly in the next step without purification. *m/z* = 442 (M+1).

Compound 84: A solution of compound **83** (1.92 g, 4.34 mmol) and aq. 3 N HCl (14.5 mL, 43.5 mmol) in MeOH (50 mL) was stirred at room temperature under nitrogen overnight. The sample was concentrated, cooled, and basified with aq. 10% NH_4OH solution (50 mL). The mixture was extracted with $CHCl_3$ (2 × 25 mL). The combined organic extract was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **84** (69 mg, 4% yield) as a yellow oil. *m/z* = 398 (M+1).

Compound 85: To a stirring solution at room temperature under nitrogen of compound **84** (69 mg, 0.17 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.16 mL, 0.85 mmol). After 16 h, the solution was concentrated, and the residue was partitioned

between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **85** (73 mg, quantitative yield) as a yellow oil, which was used in the next reaction without purification. *m/z* = 426 (M+1).

Compound 86: A mixture under nitrogen of compound **85** (73 mg, 0.17 mmol), and hydroxylamine hydrochloride (30 mg, 0.43 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The mixture was concentrated, cooled, carefully basified with aq. sat. $NaHCO_3$ (25 mL), and extracted with EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated to give compound **86** (67 mg, 93%) as a yellow oil, which was used in the next reaction without purification. *m/z* = 423 (M+1).

Compound 87: To a stirring solution at room temperature under nitrogen of compound **86** (67 mg, 0.16 mmol) in MeOH (10 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.15 mL, 0.80 mmol). The mixture was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL) dried over $MgSO_4$, filtered and concentrated to give compound **87** (62 mg, 92%) as a yellow foamy solid, which was used in the next reaction without purification. *m/z* = 423 (M+1).

T36: To a stirring solution at 0 °C under nitrogen of compound **87** (62 mg, 0.15 mmol) in DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (21 mg, 0.073 mmol) in DMF (1 mL). After stirring the mixture at 0 °C for 30 min, pyridine (0.12 mL, 1.49 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T36** (13 mg, 21%) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.81 (m, 2H), 8.35 (m, 2H), 7.28 (m, 5H), 4.20 (s, 2H), 2.99 (dd, J = 5.2, 16.0 Hz, 1H), 2.76 (ddd, J = 7.4, 11.1, 18.3 Hz, 1H), 2.58 (qd, 6.8, 13.3 Hz, 1H), 2.13 (m, 2H), 1.79 (dq, J = 6.6, 13.1 Hz, 1H), 1.47 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); *m/z* = 421 (M+1).

Compound 88: Compound **8** (10 g, 42.0 mmol) was taken up in EtOH (150 mL). 2-Fluorobenzaldehyde (4.9 mL, 46.2 mmol) and potassium fluoride on aluminum oxide (5.5 mmol/g, 11.5 g, 63.0 mmol) were added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated, mixed with hexanes. The product was precipitated, filtered and dried under vacuum to give an off-white solid compound **88** (10.8 g, 74% yield). *m/z* = 345 (M+1).

Compound 89 (MnO_2)**:** Compound **88** (4.4 g, 12.8 mmol) was taken up in EtOH (100 mL). 4-Quinolinecarboximidamide hydrochloride (4 g, 19.3 mmol) and K_2CO_3 (5.35 g, 38.7 mmol) were added. The reaction mixture was heated to reflux for 16 h. The reaction mixture was concentrated and mixed with water (50 mL), neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated. The crude product was taken up in CH_2Cl_2 (25 mL). Manganese(IV) oxide (88%, 10 g, 101.2 mmol) was added. The mixture was stirred overnight at room

temperature. The reaction mixture was filtered and concentrated. The crude residue was purified by flash chromatography (silica gel, eluted with 0 to 35% EtOAc in hexanes) to give compound **89** (6.1 g, 96% yield) as a white foamy solid. *m/z* = 496 (M+1).

Compound 89 (DDQ)**:** Compound **88** (1.10 g, 3.19 mmol), 4-quinolinecarboximidamide hydrochloride (1.00 g, 4.82 mmol) and K_2CO_3 (1.33 g, 9.62 mmol) in EtOH (25 mL) were heated at reflux under nitrogen for 16 h. The reaction mixture was concentrated, neutralized with aq. 10% NaH_2PO_4, and extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated to give the crude product as a dark green foamy solid. The crude product was dissolved in CH_2Cl_2 (21 mL). DDQ (796 mg, 3.51 mmol) was added. The reaction was stirred at room temperature for 1 h. Aq. sat. $NaHCO_3$ was added. The mixture was stirred for 5 min, and filtered through a pad of Celite®. The filtrate was extracted with CH_2Cl_2. The organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluted with 0 to 60% EtOAc in hexanes) to give compound **89** (1.43 g, 90% yield) as a white foamy solid. *m/z* = 496 (M+1).

Compound 90: Compound **89** (6.1 g, 12.3 mmol) was taken up in THF (50 mL). Aq. 3 N HCl (25 mL, 75 mmol) was added. The mixture was stirred overnight at room temperature. After concentrated, the residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **90** (5.4 g, 97% yield) as a white foamy solid. *m/z* = 452 (M+1).

Compound 91: Compound **90** (1.828 g, 4.0 mmol) was dissolved in ethyl formate (9.8 mL, 121.9 mmol) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 9.4 mL, 41.1 mmol) was added. The mixture was stirred at room temperature for 2 h, and cooled to 0 °C. Aq. HCl (6 N, 7.5 mL, 45.0 mmol) was added. The pH of the reaction mixture is ~2 (pH paper). EtOH (40 mL) and hydroxylamine hydrochloride (425 mg, 6.1 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 16 h. The reaction mixture was concentrated. EtOAc (50 mL) and aq. sat. $NaHCO_3$ (50 mL) were added. The organic extract was separated. The aqueous phase was extracted with EtOAc (20 mL). The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluted with 0% to 60% EtOAc in hexanes) to give compound **91** (1.660 g, 86% yield) as a white foamy solid. *m/z* = 477 (M+1).

Compound 92 (T186): Compound **91** (1.656 g, 3.5 mmol) was dissolved in MeOH (35 mL). Sodium methoxide (25 wt.% in methanol, 1.2 mL, 5.2 mmol) was added. The reaction mixture was stirred at 55 °C for 1.5 h. The reaction was cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4 (9.4 mL). MeOH was removed by evaporation. EtOAc (50 mL) and water (25 mL) were added. The organic extract was separated. The aqueous phase was extracted with EtOAc (20 mL). The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluted with 0% to 80% EtOAc in hexanes) to give compound **92 (T186)** (1.570 g, 95% yield) as an off-white foamy solid. *m/z* = 477 (M+1); mixture of isomers; the major isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 4.5 Hz, 1H), 8.75 (m, 1H), 8.20 (m, 1H), 8.00 (d, *J* = 4.5 Hz,

1H), 7.76 (m, 1H), 7.62 (m,1H), 7.49 (m, 2H), 7.32 (m, 1H), 7.22 (m, 1H), 3.90 (dd, J = 13.8, 5.7 Hz, 1H), 3.53 (dd, J = 13.6, 5.7 Hz, 1H), 2.85 (m, 2H), 2.59 (m, 1H), 2.32 (t, J = 13.7 Hz, 1H), 2.07 (m, 1H), 1.95 (td, J = 12.4, 2.6 Hz, 1H), 1.75 (m, 1H), 1.59 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H).

T37 (Method A)**:** Compound **92** (1.364 g, 2.8 mmol) was dissolved in anhydrous DMF (7 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (409 mg, 1.4 mmol) in DMF (7 mL) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (0.70 mL, 8.7 mmol) was added. The reaction was heated at 55 °C (oil bath) for 3 h, and cooled to room temperature. CH_2Cl_2 (50 mL) was added. The mixture was washed with water (4 × 40 mL). The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene (30 mL). The residue was purified by flash chromatography (silica gel, eluted with 0% to 80% EtOAc in hexanes) to give compound **T37** (1.190 g, 88% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.5 Hz, 1H), 8.95 (s, 1H), 8.71 (dd, J = 1.4, 8.5 Hz, 1H), 8.22 (br d, J = 8.4 Hz, 1H), 8.02 (d, J = 4.5 Hz, 1H), 7.78 (ddd, J = 1.4, 6.9, 8.4 Hz, 1H), 7.64 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.50 (m, 2H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.22 (m, 1H), 2.89 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.8, 12.8 Hz, 1H), 2.17 (m, 1H), 1.85 (ddd, J = 10.3, 15.5, 18.3 Hz, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

T37 and T38 (Method B)**:** Compound **92** (5.2 g, 10.91 mmol) was dissolved in dry DMF (10 mL), and the solution was cooled to 0 °C. Bromine (1.92 g, 12.03 mmol) in CH_2Cl_2 (2 mL) was added. The reaction was stirred at 0 °C for 2 h, and pyridine (5 mL, 61.96 mmol) was added. The reaction was heated at 50 °C for 4 h, and then concentrated. The residue was mixed with aq. $NaHCO_3$ (30 mL) and EtOAc (10 mL) and stirred for 1 h. The precipitated solid was collected by filtration and washed with water. The solid was dissolved in CH_2Cl_2, dried with $MgSO_4$, filtered, and concentrated. The crude product was mixed with EtOAc (60 mL), and heated at reflux overnight. The mixture was cooled; the precipitated solid was collected by filtration; and dried under vacuum give compound **T37** (3.1 g, 60% yield) as an off-white solid. *m/z* = 475 (M+1). The filtrate was purified by flash chromatography for three times (silica gel, 0 to 35% EtOAc in hexanes) to give compound **T38** (35 mg, 0.7% yield) as a foam. **T38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.5 Hz, 1H), 8.70 (dd, J = 0.8, 8.4 Hz, 1H), 8.65 (s, 1H), 8.23 (br d, J = 8.8 Hz, 1H), 8.02 (d, J = 4.4 Hz, 1H), 7.79 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.65 (ddd, J = 1.3, 6.8, 8.3 Hz, 1H), 7.53 (m, 2H), 7.34 (dt, J = 1.1, 7.5 Hz, 1H), 7.24 (m, 1H), 3.19 (ddd, J = 3.1, 5.0, 13.8 Hz, 1H), 2.98 (m, 2H), 2.70 (m, 1H), 2.08 (s, 3H), 1.89 (s, 3H); *m/z* = 473 (M+1).

Compound 93: Compound **9** (860 mg, 2.90 mmol) was taken up in EtOH (10 mL). Quinoline-4-carboximidamide hydrochloride (1 g, 4.81 mmol) and potassium carbonate (800 mg, 5.80) were added. The reaction mixture was stirred at room temperature for 3 days, and concentrated. The residue was mixed with water (20 mL) and EtOAc (100 mL), heated at 65 °C for 30 min, and cooled to room temperature. The mixture was extracted with EtOAc. The organic extract was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **93** (360 mg, 30% yield) as an off-white solid. *m/z* = 418 (M+1).

Compound 94 and 95: Compound **93** (345 mg, 0.83 mmol) was taken up in toluene (2 mL). Phosphorus(V) oxychloride (1.3 g, 8.48 mmol) was added. The mixture was heated in Biotage® Initiator™ microwave synthesizer at 100 °C for 30 min, cooled, and poured into ice. The mixture was extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give a mixture of compound **94** and compound **95** (300 mg) as an off-white solid. *m/z* = 436 (compound **94**, M+1) and 392 (compound **95**, M+1).

Compound 96a and 97a: A mixture of compound **94** and compound **95** (300 mg) was taken up in 1,4-dioxane (6 mL). Potassium carbonate (290 mg, 2.10 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (55 mg, 0.075 mmol) and 3-fluorophenylboronic acid (190 mg, 1.36 mmol) were added. After sparged with nitrogen for 10 min, the mixture was heated at 90 °C for 16 h, cooled, and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give a mixture of compound **96a** and **97a** (300 mg) as a foam. *m/z* = 496 (compound **96a**, M+1) and 452 (compound **97a**, M+1).

Compound 97a: A mixture of compound **96a** and **97a** (300 mg) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat.$NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **97a** (270 mg, 72% yield from compound **93**) as a foam. *m/z* = 452 (M+1).

Compound 98a: Compound **97a** (270 mg, 0.60 mmol) was taken up in ethyl formate (15 mL, 186.5 mmol). Sodium methoxide (30 wt.% in methanol, 250 mg, 1.39 mmol) was added. After stirring overnight at room temperature, the reaction mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **98a** (290 mg, quantitative yield) as a foam. *m/z* = 480 (M+1).

Compound 99a: Compound **98a** (290 mg, 0.60 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (100 mg, 1.44 mmol) was added. The reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **99a** (290 mg, quantitative yield) as a foam. *m/z* = 477 (M+1).

Compound 100a: Compound **99a** (290 mg, 0.60 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in methanol, 250 mg, 1.39 mmol) was added. The reaction mixture was stirred at room temperature overnight, and neutralized by the addition of aq. sat. KH_2PO_4. The mixture was extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated to give compound **100a** (290 mg, quantitative yield) as a foam. *m/z* = 477 (M+1).

T39: Compound **100a** (290 mg, 0.60 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (110 mg, 0.69 mmol) in CH_2Cl_2 (1 mL) was added. The reaction was stirred at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added. The reaction was allowed to warm to room

temperature, stirred at 50 °C for 16 h, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T39** (80 mg, 28% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.4 Hz, 1H), 8.93 (s, 1H), 8.71 (dd, J = 1.4, 8.7 Hz, 1H), 8.23 (dd, J = 1.5, 8.8 Hz, 1H), 8.02 (d, J = 4.4 Hz, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.64 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.51 (dt, J = 5.7, 8.0 Hz, 1H), 7.41 (td, J = 1.3, 7.7 Hz, 1H), 7.35 (ddd, J = 1.5, 2.6, 9.4 Hz, 1H), 7.22 (ddt, J = 1.0, 2.6, 8.3 Hz, 1H), 3.04 (m, 2H), 2.65 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.21 (tdd, J = 2.9, 6.0, 14.0 Hz, 1H), 1.85 (m, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 96b and 97b: A mixture of compound **94** and compound **95** (300 mg) was taken up in 1,4-dioxane (6 mL). Potassium carbonate (290 mg, 2.10 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (55 mg, 0.075 mmol) and 4-fluorophenylboronic acid (190 mg, 1.36 mmol) were added. After sparged with nitrogen for 10 min, the mixture was heated at 90 °C for 16 h, cooled, and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, 0 to 30% EtOAc in hexanes) to give a mixture of compound **96b** and **97b** (340 mg) as a foam. *m/z* = 496 (compound **96b**, M+1) and 452 (compound **97b**, M+1).

Compound 97b: A mixture of compound **96b** and **97b** (340 mg) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **97b** (310 mg, 83% yield from compound **93**) as a foam. *m/z* = 452 (M+1).

Compound 98b: Compound **97b** (310 mg, 0.69 mmol) was taken up in ethyl formate (15 mL, 186.5 mmol). Sodium methoxide (30 wt.% in methanol, 400 mg, 2.22 mmol) was added. After stirring overnight at room temperature, the reaction mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **98b** (330 mg, quantitative yield). *m/z* = 480 (M+1).

Compound 99b: Compound **98b** (330 mg, 0.69 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (100 mg, 1.44 mmol) was added. The reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **99b** (330 mg, quantitative yield) as a foam. *m/z* = 477 (M+1).

Compound 100b: Compound **99b** (330 mg, 0.69 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in methanol, 400 mg, 2.22 mmol) was added. The reaction mixture was stirred at room temperature overnight, and neutralized by the addition of aq. sat. KH_2PO_4. The mixture was extracted with EtOAc. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **100b** (330 mg, quantitative yield) as a foam. *m/z* = 477 (M+1).

T40: Compound **100b** (330 mg, 0.69 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (110 mg, 0.69 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction stirred

at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added, and the reaction was allowed to warm to room temperature, stirred at 50 °C for 16 h, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **T40** (55 mg, 17% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.4 Hz, 1H), 8.94 (s, 1H), 8.71 (dd, J = 1.3, 8.6 Hz, 1H), 8.23 (d, J = 0.8, 8.4 Hz, 1H), 8.02 (d, J = 4.5 Hz, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.65 (m, 3H), 7.23 (m, 2H), 3.05 (m, 2H), 2.65 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.21 (tdd, J = 3.2, 6.3, 14.1 Hz, 1H), 1.84 (ddt, J = 7.3, 10.4, 13.4 Hz, 1H), 1.59 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 101 and 102: A mixture of compound **94** and compound **95** (300 mg) was taken up in THF (4 mL). A solution of sodium hydride (60 % dispersion in mineral oil, 115 mg, 2.88 mmol), and 2-propanol (1 g, 16.6 mmol) in THF (5 mL) was added. The mixture was stirred at room temperature for 1 h, and concentrated. The residue was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give a mixture of compound **101** and **102** (300 mg). *m/z* = 460 (compound **101**, M+1) and 416 (compound **102**, M+1).

Compound 102: A mixture of compound **101** and **102** (300 mg) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give compound **102** (270 mg, 78% yield from compound **93**) as a foam. *m/z* = 416 (M+1).

Compound 103: Compound **102** (270 mg, 0.65 mmol) was taken up in ethyl formate (15 mL, 186.5 mmol). Sodium methoxide (30 wt.% in methanol, 250 mg, 1.39 mmol) was added. After stirring overnight at room temperature, the reaction mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **103** (290 mg, quantitative yield) as a foam. *m/z* = 444 (M+1).

Compound 104: Compound **103** (290 mg, 0.65 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (100 mg, 1.44 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **104** (290 mg, quantitative yield) as a foam. m/z = 441 (M+1).

Compound 105: Compound **104** (290 mg, 0.65 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in methanol, 250 mg, 1.39 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **105** (260 mg, 91% yield) as a foam. *m/z* = 441 (M+1).

T41: Compound **105** (260 mg, 0.59 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (110 mg, 0.69 mmol) in CH_2Cl_2 (1 ml) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added. The reaction was allowed to warm to room temperature, stirred at 50 °C for 16 h, and concentrated. The residue was purified by flash

chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T41** (25 mg, 10% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 4.5 Hz, 1H), 8.39 (s, 1H), 8.76 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 4.5 Hz, 1H), 7.77 (t, J = 7.2 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 5.53 (septet, J = 6.2 Hz, 1H), 2.92 (dd, J = 6.7, 18.8 Hz, 1H), 2.66 (m, 2H), 2.20 (m, 2H), 1.82 (m, 1H), 1.52 (s, 3H), 1.44 (d, J = 6.3 Hz, 3H), 1.42 (d, J = 6.3 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 439 (M+1).

Compound 106 and 107: A mixture of compound **94** and compound **95** (410 mg, ~0.94 mmol) was taken up in 1,4-dioxane (6 mL). Potassium carbonate (400 mg, 2.99 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (70 mg, 0.095 mmol) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (320 mg, 1.90 mmol) were added. After sparged with nitrogen for 10 min, the mixture was heated at 90 °C for 16 h, cooled, and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give a mixture of compound **106** and **107** (410 mg, quantitative yield) as a foam. *m/z* = 442 (compound **106**, M+1) and 398 (compound **107**, M+1).

Compound 108 and 109: A mixture of compound **106** and **107** (410 mg, ~0.93 mmol) and 10% palladium on carbon (35 mg) in THF (15 mL) was hydrogenated at atmospheric pressure for 16 h at room temperature. The reaction mixture was filtered through a Celite® pad. The filtrate was concentrated to give a mixture of compound **108** and **109** (410 mg, quantitative yield) as a foam. *m/z* = 444 (compound **108**, M+1) and 400 (compound **109**, M+1).

Compound 109: A mixture of compound **108** and **109** (410 mg, ~0.93 mmol) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give compound **109** (270 mg, 72% yield) as a foam. *m/z* = 400 (M+1).

Compound 110: Compound **109** (270 mg, 0.67 mmol) was taken up in ethyl formate (15 mL, 186.5 mmol). Sodium methoxide (30 wt.% in methanol, 400 mg, 2.22 mmol) was added. After stirring overnight at room temperature, the reaction mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give compound **110** (290 mg, quantitative yield) as a foam. *m/z* = 428 (M+1).

Compound 111: Compound **110** (290 mg, 0.67 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (100 mg, 1.44 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated to give compound **111** (275 mg, 95% yield) as a foam. *m/z* = 425 (M+1).

Compound 112: Compound **111** (275 mg, 0.65 mmol) was dissolved in THF (5 mL), and sodium methoxide (30 wt.% in methanol, 400 mg, 2.22 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and

extracted with EtOAc. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **112** (250 mg, 91% yield) as a foam. *m/z* = 425 (M+1).

T42: Compound **112** (250 mg, 0.59 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (105 mg, 0.66 mmol) in CH_2Cl_2 (1 ml) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added. The reaction was allowed to warm to room temperature, stirred at 50 °C for 16 h, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **T42** (45 mg, 18% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 4.5 Hz, 1H), 8.94 (s, 1H), 8.83 (d, J = 1.4, 8.8 Hz, 1H), 8.22 (dd, J = 1.2, 8.6 Hz, 1H), 8.05 (d, J = 4.5 Hz, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.63 (ddd, J = 1.4, 6.8, 8.2 Hz, 1H), 3.32 (septet, J = 6.7 Hz, 1H), 3.11 (dd, J = 6.7, 18.2 Hz, 1H), 2.94 (ddd, J = 7.4, 11.1, 18.2 Hz, 1H), 2.63 (qd, J = 6.7, 13.3 Hz, 1H), 2.23 (m, 2H), 1.89 (m, 1H), 1.54 (s, 3H), 1.40 (d, J = 6.6 Hz, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H); *m/z* = 423 (M+1).

Compound 113: In a sealable vial, a mixture of compound **65** (175 mg, 0.513 mmol), 2-methylpyridine-4-boronic acid (105 mg, 0.767 mmol) and potassium carbonate (210 mg, 1.52 mmol) in 1,4-dioxane (6 mL) and DMF (2 mL) was degassed. [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (38 mg, 0.052 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C for 16 h. The dark mixture was cooled, diluted with EtOAc (50 mL), stirred for 30 min, and filtered through a pad of Celite®. The filtrate was washed with aq. sat. KH_2PO_4 (50 mL) and brine (50 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **113** (154 mg, 75% yield) as a tan foamy solid. *m/z* = 398 (M+1).

Compound 114: To a stirring solution at room temperature under nitrogen of compound **113** (154 mg, 0.387 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.36 mL, 1.92 mmol). After stirring for 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **114** (162 mg, 98% yield) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 426 (M+1).

Compound 115: A mixture under nitrogen of compound **114** (162 mg, 0.381 mmol) and hydroxylamine hydrochloride (67 mg, 0.964 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and then stirred at room temperature overnight. The solution was concentrated, cooled, carefully basified with aq. sat. $NaHCO_3$ (25 mL) and extracted with EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **115** (156 mg, 97% yield) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 423 (M+1).

Compound 116: To a stirring solution at room temperature under nitrogen of compound **115** (156 mg, 0.369 mmol) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.35 mL, 1.86 mmol). The mixture was stirred at room temperature overnight, and concentrated. The residue

was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **116** (104 mg, 67% yield) as an off-white foamy solid. *m/z*= 423 (M+1).

T43: To a stirring solution at 0 °C under nitrogen of compound **116** (104 mg, 0.245 mmol) in DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (35 mg, 0.122 mmol) in DMF (1 mL). After stirring at 0 °C for 30 min, pyridine (0.20 mL, 2.48 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T43** (28 mg, 27% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.67 (d, J = 5.2, 1H), 8.22 (s, 1H), 8.17 (d, J = 5.2 Hz, 1H), 7.60 (m, 2H), 7.53 (m, 3H), 2.99 (m, 2H), 2.70 (s, 3H), 2.63 (qd, J = 6.8, 13.4 Hz, 1H), 2.27 (dt, J = 2.7, 12.8 Hz, 1H), 2.15 (m, 1H), 1.79 (m, 1H), 1.54 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 421 (M+1).

Compound 117: In a sealable vial, a mixture of compound **65** (403 mg, 1.18 mmol), *N*-Boc-1,2,3,6-tetrahydropyridine-4-boronic acid pinacol ester (550 mg, 1.78 mmol) and potassium phosphate (750 mg, 3.53 mmol) in 1,4-dioxane (12 mL) was degassed. Tetrakis(triphenylphosphine)palladium(0) (140 mg, 0.12 mmol) was added, and the mixture was degassed again. The vial was sealed and heated at 90 °C overnight. The mixture was cooled, diluted with EtOAc (50 mL), stirred for 30 min, and filtered through a pad of Celite®. The filtrated was washed with aq. sat. KH_2PO_4 (50 mL) and brine (50 mL). The organic extract was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 5% EtOAc in CH_2Cl_2) to give compound **117** (724 mg) as a yellow foamy solid, which was used in the next reaction without additional purification. *m/z* = 488 (M+1).

Compound 118: A mixture of compound **117** (all from the last step) and 10% palladium on carbon (70 mg) in EtOAc (25 mL) was hydrogenated (balloon pressure) at room temperature overnight. Additional amount of 10% palladium on carbon (100 mg) was added, and the mixture was hydrogenated (balloon pressure) at room temperature for another overnight. The mixture was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give compound **118** (334 mg, 58% yield from compound **65**) as an off-white solid. *m/z* = 490 (M+1).

Compound 119: To a stirring solution at room temperature under nitrogen of compound **118** (334 mg, 0.68 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.64 mL, 3.41 mmol). After stirring for 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **119** (356 mg,

quantitative yield) as an off-white foamy solid, which was used in the next reaction without purification. *m/z* = 518 (M+1).

Compound 120: A mixture under nitrogen of compound **119** (356 mg, 0.68 mmol) and hydroxylamine hydrochloride (71 mg, 1.02 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and stirred at room temperature overnight. The solution was concentrated, cooled, carefully basified with aq. sat. $NaHCO_3$ (25 mL) and extracted with EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **120** (305 mg, 87% yield) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 515 (M+1).

Compound 121: To a stirring solution at room temperature under nitrogen of compound **120** (305 mg, 0.59 mmol) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.56 mL, 2.98 mmol). The mixture was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **121** (273 mg, 89% yield) as a tan foamy solid. *m/z* = 515 (M+1).

T44: To a stirring solution at 0 °C under nitrogen of compound **121** (273 mg, 0.53 mmol) in DMF (8 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (76 mg, 0.26 mmol) in DMF (2 mL). After stirring the mixture at 0 °C for 30 min, pyridine (0.43 mL, 5.32 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T44** (164 mg, 60% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.48 (m, 5H), 4.24 (br s, 2H), 3.07 (tt, J = 3.6, 11.6 Hz, 1H), 2.89 (m, 4H), 2.58 (m, 1H), 2.19 (dt, J = 2.8, 12.8 Hz, 1H), 2.07 (m, 3H), 1.88 (m, 2H), 1.72 (m, 1H), 1.49 (s, 9H), 1.46 (s, 3H), 1.30 (d, J = 7.2 Hz, 3H); *m/z* = 457 (M-C_4H_7).

T45: A solution of **T44** (140 mg, 0.27 mmol) in CH_2Cl_2 (20 mL) at room temperature under nitrogen was treated with hydrogen chloride (4 N solution in 1,4-dioxane, 0.70 mL, 2.8 mmol). The mixture was stirred for 4 h and concentrated to a gummy solid, which was triturated with Et_2O, filtered and vacuum dried to give compound **T45** (101 mg, 83% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (br s, 1H), 9.49 (br s, 1H), 8.86 (s, 1H), 7.47 (m, 5H), 3.59 (m, 2H), 3.19 (m, 3H), 2.89 (m, 2H), 2.57 (m, 1H), 2.44 (m, 4H), 2.20 (br t, J = 12.0 Hz, 1H), 2.09 (m, 1H), 1.72 (m, 1H), 1.46 (s, 3H), 1.29 (d, J = 6.4 Hz, 3H); *m/z* = 413 (M+1).

T46: A mixture of **T45** (48 mg, 0.11 mmol) and sodium acetate (88 mg, 1.07 mmol) in acetic anhydride (1 mL, 10.58 mmol) was stirred at room temperature under nitrogen for 48 h. The mixture was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **T46** (34 mg, 69% yield) as an off-white foamy solid. **T46** is a 1:1 mixture of amide isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ [8.90 (s), 8.88 (s), 1:1, 1H], 7.48 (m, 5H), 4.75 (br d, J = 14.3

Hz, 1H), 3.97 (br t, J = 13.0 Hz, 1H), 3.22 (m, 2H), 2.82 (m, 3H), 2.58 (m, 1H), [2.17 (s), 2.15 (s), 1:1, 3H], 1.94 (m, 7H), 1.46 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); *m/z* = 455 (M+1).

Compound 122: In a sealable vial, a mixture of compound **65** (287 mg, 0.842 mmol), *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(*2H*)-carboxylate (260 mg, 0.841 mmol) and potassium phosphate (750 mg, 3.53 mmol) in 1,4-dioxane (10 mL) was degassed. [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (62 mg, 0.085 mmol) was added, and the mixture degassed again. The vial was sealed and heated at 90 °C overnight. The mixture was cooled, diluted with EtOAc (50 mL), stirred for 30 min, and then filtered through a pad of Celite®. The filtrate was washed with aq. sat. KH_2PO_4 (50 mL) and brine (50 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 10% EtOAc in CH_2Cl_2) to give compound **122** (220 mg, 54% yield) as an off-white foamy solid. *m/z* = 488 (M+1).

Compound 123: To a stirring solution at room temperature under nitrogen of compound **122** (220 mg, 0.451 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.42 mL, 2.24 mmol). After stirring for 16 h, the solution was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **123** (250 mg) as a yellow oil, which was used in the next reaction without purification. *m/z* = 516 (M+1).

Compound 124: A mixture under nitrogen of compound **123** (all from the last step) and hydroxylamine hydrochloride (47 mg, 0.676 mmol) in EtOH (20 mL) was heated at 60 °C for 2 h, and stirred at room temperature overnight. The solution was concentrated, cooled, carefully basified with aq. sat. $NaHCO_3$ (25 mL) and extracted with EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **124** (181 mg, 78% from compound **122**) as a tan foamy solid, which was used in the next reaction without purification. *m/z* = 513 (M+1).

Compound 125: To a stirring solution at room temperature under nitrogen of compound **124** (181 mg, 0.353 mmol) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.33 mL, 1.76 mmol). The mixture was stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **125** (139 mg, 77% yield) as a yellow foamy solid, which was used in the next reaction without purification. *m/z* = 513 (M+1).

T47: To a stirring solution at 0 °C under nitrogen of compound **125** (139 mg, 0.271 mmol) in DMF (8 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (51 mg, 0.178 mmol) in DMF (2 mL). After stirring at 0 °C for 30 min, pyridine (0.29 mL, 3.59 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give compound **T47** (55 mg, 40%

yield) as light a yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.49 (m, 6H), 4.54 (m, 1H), 3.60 (m, 2H), 2.92 (m, 2H), 2.58 (qd, J = 6.7, 13.3 Hz, 1H), 2.42 (m, 2H), 2.20 (dt, J = 2.6, 12.8 Hz, 1H), 2.08 (m, 2H), 1.72 (m, 1H), 1.51 (s, 9H), 1.46 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); *m/z* = 511 (M+1).

T48: A solution of **T47** (42 mg, 0.082 mmol) in CH_2Cl_2 (10 mL) at room temperature under nitrogen was treated with hydrogen chloride (4 N solution in 1,4-dioxane, 0.40 mL, 1.60 mmol). The mixture was stirred for 16 h and concentrated to a gummy solid, which was triturated with Et_2O, filtered and vacuum dried to give compound **T48** (37 mg, quantitative yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ10.21 (br s, 1H), 10.13 (br s, 1H), 8.84 (s, 1H), 7.57 (m, 1H), 7.48 (m, 5H), 4.36 (m, 2H), 3.41 (m, 2H), 2.89 (m, 4H), 2.59 (qd, J = 6.6, 13.3 Hz, 1H), 2.21 (t, J = 12.6 Hz, 1H), 2.07 (m, 1H), 1.71 (m, 1H), 1.46 (s, 3H), 1.31 (d, J = 6.7 Hz, 3H); *m/z* = 411 (M+1).

T49: A mixture of **T48** (32 mg, 0.071 mmol) and sodium acetate (60 mg, 0.73 mmol) in acetic anhydride (1 mL, 10.58 mmol) was stirred at room temperature under nitrogen for 48 h. The mixture was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **T49** (11 mg, 34% yield) as a light yellow foamy solid. **T49** is a 1:1 mixture of amide isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ [8.91 (s), 8.88 (s), 1:1, 1H], 7.50 (m, 6H), [4.78 (dd, J = 2.6, 18.6 Hz), 4.62 (dd, J = 2.6, 18.6 Hz), 1:1, 1H], 4.54 (m, 1H), 3.79 (m, 1H), 3.62 (m, 1H), 2.91 (m, 2H), 2.58 (m, 1H), 2.46 (m, 2H), [2.22 (s), 2.19 (s), 1:1, 3H], 2.14 (m, 2H), 1.73 (m, 1H), 1.48 (s, 3H), [1.31 (d, J = 6.7 Hz), 1.30 (d, J = 6.7 Hz), 1:1, 3H]; *m/z* = 453 (M+1).

Compound 126: In a pressure vessel, a mixture of compound **8** (5.00 g, 20.98 mmol), 4-fluorobenzaldehyde (6.7 mL, 62.4 mmol) and potassium fluoride on aluminum oxide (5.5 mmol/g, 7.6 g, 41.8 mmol) in 2-propanol (42 mL) was flushed with nitrogen, and sealed. After heated at 60 °C for 4 h, and stirred at room temperature overnight, the mixture was filtered through a pad of Celite®. The filtrate was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (100 mL) and EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give compound **126** (6.28 g, 87% yield) as a light yellow solid. *m/z* = 345 (M+1).

Compound 127: A mixture of compound **126** (7.34 g, 21.31 mmol), 2-methyl-4-pyridinecarboximidamide hydrochloride (Bolli, *et al.*, 2003) (5.50 g, 32.04 mmol) and potassium carbonate (7.4 g, 53.5 mmol) in EtOH (43 mL) was refluxed under nitrogen for 48 h. The mixture was cooled to room temperature, filtered through a pad of Celite® and the solid was washed with EtOH (100 mL). The combined filtrate and wash was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (100 mL) and $CHCl_3$ (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to give the crude dihydropyrimidine (12.38 g) as a bright yellow solid. *m/z* = 462 (M+1).

A mixture of the crude dihydropyrimidine (12.38 g) and manganese(IV) oxide (88%, 9.26 g, 93.73 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature under nitrogen overnight. The mixture was filtered through a pad of Celite®. The filtrate was concentrated and the residue was purified by flash

chromatography (silica gel, eluting with 20% to 50% EtOAc in hexanes) to give compound **127** (8.72 g, 89% yield) as a gummy light yellow foamy solid. *m/z* = 460 (M+1).

Compound 128: A solution of compound **127** (8.72 g, 18.98 mmol) in MeOH (63 mL) was treated with aq. 3 N HCl solution (63 mL, 189 mmol). After stirring at room temperature under nitrogen overnight, the mixture was concentrated, cooled, basified with concentrated ammonium hydroxide to pH ~ 9-10, and then extracted with $CHCl_3$ (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give compound **128** (8.57 g, quantitative yield) as a light yellow foamy solid. *m/z* = 416 (M+1).

Compound 129: To a stirring solution at 0 °C (under a drying tube) of compound **128** (all from the last step) in ethyl formate (80 mL) was added dropwise sodium methoxide (30 wt.% solution in MeOH, 17.6 mL, 94.8 mmol). After addition, the ice-bath was removed and the mixture was stirred at room temperature overnight. The resultant orange-brown suspension was concentrated, and the residue was partitioned between aq. sat. KH_2PO_4 (150 mL) and EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give compound **129** (8.26 g, 98% yield) as an orange-pink foamy solid. *m/z* = 444 (M+1).

Compound 130: To a stirring solution at room temperature under nitrogen of compound **129** (8.26 g, 18.64 mmol) and acetic acid (10.7 mL, 186.9 mmol) in EtOH (93 mL) was added hydroxylamine hydrochloride (1.94 g, 27.92 mmol). The mixture was heated at 60 °C for 4 h, and then stirred at room temperature overnight. After concentration, the residue was partitioned between aq. 10% NH_4OH (100 mL) and $CHCl_3$ (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give compound **130** (9.23 g, quantitative yield) as a brown foamy solid. *m/z* = 441 (M+1).

Compound 131 (T187): A mixture of compound **130** (all from the last step) and potassium carbonate (5.5 g, 39.8 mmol) in MeOH (79 mL) was stirred at room temperature under nitrogen overnight. The mixture was concentrated, and the residue was partitioned between Et_2O (50 mL) and water (50 mL). The basic aqueous extract was cooled, acidified with aq. sat. KH_2PO_4 (150 mL), and then extracted with EtOAc (2 × 100 mL). The combined organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **131 (T187)** (5.63 g, 68% yield) as a yellow foamy solid. *m/z* = 441 (M+1); mixture of isomers; the major isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 5.2, 0.9 Hz, 1H), 8.16 (s, 1H), 8.12 (ddd, *J* = 5.3, 1.7, 0.7 Hz, 1H), 7.61 (m, 2H), 7.20 (m, 2H), 3.92 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.59 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.93 (m, 2H), 2.68 (s, 3H), 2.60 (dq, *J* = 12.8, 6.4 Hz, 1H), 2.26 (t, *J* = 13.7 Hz, 1H), 2.07 (m, 1H), 1.89 (td, *J* = 12.5, 2.6 Hz, 1H), 1.68 (m, 1H), 1.53 (s, 3H), 1.20 (d, *J* − 6.4 Hz, 3H).

T50: To a stirring solution at 0 °C under nitrogen of compound **131** (5.56 g, 12.62 mmol) in degassed DMF (50 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (1.98 g, 6.92 mmol) in degassed DMF (10 mL). After stirring at 0 °C for 30 min, pyridine (10.2 mL, 126.4 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and

concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (200 mL) and $CHCl_3$ (200 mL). The organic extract was washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% to 100% EtOAc in hexanes) to give partially purified product. The sample was suspended in degassed EtOH (100 mL), stirred at room temperature for 30 min, and then concentrated to dryness. This process was repeated twice. In the third time, the mixture was concentrated to 25 mL, cooled and filtered. The solid was washed with cold degassed EtOH, and vacuum dried to give compound **T50** (3.25 g, 59% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.68 (d, J = 5.1 Hz, 1H), 8.20 (s, 1H), 8.15 (dd, J = 1.6, 5.2 Hz, 1H), 7.63 (m, 2H), 7.22 (m, 2H), 2.97 (m, 2H), 2.71 (s, 3H), 2.63 (qd, J = 6.7, 13.4 Hz, 1H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.16 (tdd, J = 2.6, 5.8, 13.6 Hz, 1H), 1.79 (m, 1H), 1.54 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 439 (M+1).

Compound 132: In a sealable vial, a mixture of compound **9** (2.61 g, 8.81mmol), 2-methyl-4-pyridinecarboximidamide hydrochloride (1.80 g, 10.49 mmol) and potassium carbonate (2.9 g, 21.0 mmol) in EtOH (9 mL) was flushed with nitrogen, sealed and stirred at room temperature for 5 days. The mixture was concentrated. The residue was diluted with EtOAc (150 mL) and water (50 mL) and heated at 65 °C until all solid was in solution (15 min). The layers were separated. The organic extract was washed with aq. sat. KH_2PO_4 (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 5% MeOH in EtOAc) to give compound **132** (2.00 g, 60% yield) as a light yellow solid. *m/z* = 382 (M+1).

Compound 133: In a microwave vessel, a mixture of compound **132** (1.00 g, 2.62 mmol) and phosphorus(V) oxychloride (2.4 mL, 25.4 mmol) in toluene (10 mL) was flushed with nitrogen. The vial was sealed, and heated in Biotage® microwave synthesizer at 100 °C for 1 h. The mixture was cooled to room temperature, and then carefully poured into a stirring solution of $NaHCO_3$ (11 g, 131 mmol) in water (100 mL). After stirring for 30 min, the mixture was extracted with EtOAc (2 × 100 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give a mixture of ketone and ketal (1.14 g). The sample was mixed with aq. 3 N HCl (8.7 mL, 26.1 mmol) in MeOH (20 mL), and stirred at room temperature overnight. The mixture was concentrated, cooled, basified with aq. 10% NH_4OH, and then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes) to give compound **133** (0.81 g, 87% yield) as a light yellow solid. *m/z* = 356 (M+1).

Compound 134: In a sealable vial, a mixture of compound **133** (0.37 g, 1.04 mmol), 2-fluorophenylboronic acid (0.22 g, 1.56 mmol), potassium phosphate (0.66 g, 3.11 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol) in 1,4-dioxane (10 mL) was degassed with nitrogen. The vial was sealed, and heated at 90 °C for 16 h. The mixture was cooled, and then partitioned between aq. 1 N NaOH solution (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was

purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **134** (0.47 g, quantitative yield) as a light yellow oil. *m/z* = 416 (M+1).

Compound 135: To a stirring solution at room temperature of compound **134** (all from the last step) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.97 mL, 5.17 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **135** (0.41 g, 89% yield) as a yellow oil. *m/z* = 444 (M+1).

Compound 136: To a solution of compound **135** (0.41 g, 0.92 mmol) in EtOH (20 mL) was added acetic acid (0.53 mL, 9.26 mmol) and hydroxylamine hydrochloride (0.10 g, 1.44 mmol). The mixture was heated at 60 °C under nitrogen for 2 h, and stirred at room temperature overnight. The mixture was concentrated, and the residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **136** (0.38 g, 93% yield) as a yellow foamy solid. *m/z* = 441 (M+1).

Compound 137: To a solution of compound **136** (0.34 g, 0.77 mmol) in MeOH (20 mL) was added sodium methoxide (30 wt.% solution in MeOH, 0.72 mL, 3.84 mmol). The mixture was stirred at room temperature under nitrogen for 16 h, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **137** (0.24 g, 71% yield) as a light yellow foamy solid. *m/z* = 441 (M+1).

T51: To a stirring solution at 0 °C under nitrogen of compound **137** (0.24 g, 0.54 mmol) in degassed DMF (8 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.077 g, 0.27 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (0.44 mL, 5.44 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T51** (0.13 g, 55% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.67 (d, J = 4.8 Hz, 1H), 8.19 (br s, 1H), 8.15 (dd, J = 1.2, 4.2 Hz, 1H), 7.52 (m, 1H), 7.45 (dt, J = 2.0, 7.6 Hz, 1H), 7.35 (tt, J = 1.2, 7.6, 1H), 7.22 (br t, J = 8.8 Hz, 1H), 2.81 (m, 2H), 2.70 (s, 3H), 2.62 (m, 1H), 2.26 (dt, J = 2.8, 12.8 Hz, 1H), 2.13 (m, 1H), 1.82 (m, 1H), 1.55 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H); *m/z* = 439 (M+1).

Compound 138: In a pressure vessel, a mixture of compound **8** (2.50 g, 10.49 mmol), 2,4-difluorobenzaldehyde (1.72 mL, 15.72 mmol) and potassium fluoride (40 wt.% on alumina, 3.0 g, 20.65 mmol) in 2-propanol (21 mL) was flushed with nitrogen. The vial was sealed, heated at 60 °C for 4 h, and stirred at room temperature overnight. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 solution (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and

concentrated. The crude product was triturated with hexanes (50 mL), filtered and vacuum dried to give compound **138** (1.93 g, 51% yield) as a light yellow solid. *m/z* = 363 (M+1, 100%).

Compound 139: Step 1. A mixture of compound **138** (2.22 g, 6.12 mmol), 4-quinolinecarboximidamide hydrochloride (1.91 g, 9.20 mmol) and potassium carbonate (2.5 g, 18.4 mmol) in EtOH (61 mL) was refluxed under nitrogen for 48 h. The mixture was cooled to room temperature, filtered through a pad of Celite® and the solid was washed with EtOH (100 mL). The combined filtrate and wash was concentrated, and the residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give crude dihydropyrimidine (3.0 g) as a bright yellow foamy solid. *m/z* = 516 (M+1).

A mixture of the crude dihydropyrimidine (3.0 g) and manganese(IV) oxide (88%, 3.0 g, 30.4 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature under nitrogen overnight. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **139** (2.39 g, 76% yield) as a light yellow foamy solid. *m/z* 514 (M+1).

Compound 140: A solution of compound **139** (2.39 g, 4.65 mmol) in MeOH (47 mL) was treated with aq. 3 N HCl (16 mL, 48 mmol). The mixture was stirred at room temperature under nitrogen overnight and concentrated. The residue was cooled, basified with concentrated ammonium hydroxide to pH ~ 9-10, and then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **140** (2.38 g, quantitative yield) as a light yellow foamy solid. *m/z* = 470 (M+1).

Compound 141: To a stirring solution at 0 °C (under a drying tube) of compound **140** (all from the last step) in ethyl formate (20 mL) was added dropwise sodium methoxide (30 wt.% solution in MeOH, 2.6 mL, 13.9 mmol). After addition, the ice-bath was removed. The mixture was stirred at room temperature for 2 h, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **141** (2.69 g, quantitative yield) as a dark yellow oil. *m/z* = 498 (M+1).

Compound 142: To a stirring solution at room temperature under nitrogen of compound **141** (all from the last step) and acetic acid (2.7 mL, 47.2 mmol) in EtOH (46 mL) was added hydroxylamine hydrochloride (0.49 g, 7.05 mmol). The mixture was heated at 60 °C for 4 h, stirred at room temperature overnight, and concentrated. The residue was carefully partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **142** (2.21 g, 96% yield) as an orange-dark yellow foamy solid. *m/z* = 495 (M+1).

Compound 143: A mixture of compound **142** (2.21 g, 4.47 mmol) and potassium carbonate (3.1 g, 22.4 mmol) in MeOH (45 mL) was stirred at room temperature under nitrogen overnight, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude

product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **143** (1.54 g, 69% yield) as a yellow foamy solid. *m/z* = 495 (M+1).

T52: To a stirring solution at 0 °C under nitrogen of compound **143** (1.54 g, 3.11 mmol) in degassed DMF (10 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.49 g, 1.71 mmol) in degassed DMF (2 mL). After stirring at 0 °C for 30 min, pyridine (2.5 mL, 31.0 mmol) was added. The ice-bath was removed. The sample was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give partially purified product. The sample was dissolved into CH_2Cl_2 (20 mL). Degassed EtOH (20 mL) was added. The mixture was concentrated to remove most of the CH_2Cl_2, and cooled. The precipitate was collected by filtration, and vacuum dried to give compound **T52** (0.73 g, 48% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.4 Hz, 1H), 8.93 (s, 1H), 8.68 (dd, J = 0.8, 8.6 Hz, 1H), 8.22 (dd, J = 0.8, 8.6 Hz, 1H), 8.01 (d, J = 4.4 Hz, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.64 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.49 (dt, J = 6.3, 8.4 Hz, 1H), 7.08 (m, 1H), 7.00 (ddd, J = 2.5, 8.7, 10.2 Hz, 1H), 2.87 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.7 Hz, 1H), 2.19 (m, 1H), 1.87 (m, 1H), 1.60 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 493 (M+1).

Compound 144: Compound **88** (1.08 g, 3.14 mmol), 2-chloropyridine-4-carboximidamide hydrochloride (900 mg, 4.69 mmol) and K_2CO_3 (1.30 g, 9.42 mmol) in EtOH (15 mL) were heated in a Biotage® microwave synthesizer at 120 °C for 3 h. After the reaction was cooled to room temperature, MTBE was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give the product (914 mg, 61% yield) as a yellow foamy solid. The product (903 mg, 1.88 mmol) was dissolved in CH_2Cl_2 (18 mL). DDQ (510 mg, 2.25 mmol) was added. The reaction was stirred at room temperature for 1 h. MTBE and Aq. sat. $NaHCO_3$ were added, and the mixture was stirred for 5 min. The product was extracted with MTBE. The combined organic extract was washed with aq. sat. $NaHCO_3$, and water, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% EtOAc in hexanes) to give compound **144** (832 g, 92% yield) as a white foamy solid. *m/z* = 480 (M+1).

Compound 145: A mixture of compound **144** (300 mg, 0.63 mmol), cyclopropylboronic acid (90 mg, 1.05 mmol), potassium phosphate (660 mg, 3.11 mmol), tricyclohexylphosphine (54 mg, 0.19 mmol), palladium acetate (24 mg, 0.11 mmol), toluene (4 mL) and water (0.2 mL) in a vial was sparged with nitrogen for 5 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 130 °C for 4 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was washed with water. The aqueous phase was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give the compound **145** (254 mg, 84% yield) as a white solid. *m/z* = 486 (M+1).

Compound 146: Compound **145** (306 mg, 0.63 mmol) was taken up in THF (2.1 mL) and MeOH (2.1 mL). Aq. 3 N HCl (2.1 mL, 6.3 mmol) was added. The mixture was stirred overnight at room temperature. After concentrated, the residue was neutralized with aq. sat. $NaHCO_3$ to pH ~8, and extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated to give compound **146** (296 mg) as a white foamy solid. *m/z* = 442 (M+1).

Compound 147: Compound **146** (all from above) was dissolved in ethyl formate (1.6 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 2.3 mL, 9.96 mmol) was added. The mixture was stirred at room temperature for 2 h, and cooled to 0 °C. Aq. 6 N HCl (1.7 mL, 10.2 mmol), EtOH (6.6 mL) and hydroxylamine hydrochloride (71 mg, 1.02 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. EtOAc was added. The mixture was washed with water. The aqueous phase was treated with aq. sat. $NaHCO_3$, and extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **147** (242 mg, 82% yield from compound **145**) as a white foamy solid. *m/z* = 467 (M+1).

Compound 148: Compound **147** (240 mg, 0.52 mmol) was dissolved in MeOH (2.6 mL). Sodium methoxide (25 wt.% in methanol, 0.18 mL, 0.78 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **148** (224 mg, 93% yield) as a white foamy solid. *m/z* = 467 (M+1).

T53: Compound **148** (224 mg, 0.48 mmol) was dissolved in anhydrous DMF (2 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (72 mg, 0.25 mmol) in DMF (0.5 mL) was added. The reaction was stirred at 0 °C for 1.5 h. Pyridine (120 μL, 1.49 mmol) was added. The reaction was heated at 55 °C (oil bath) for 2.5 h, and cooled to room temperature. EtOAc was added. The mixture was washed with water, aq. sat. $NaHCO_3$, and aq. 10% Na_2SO_3. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 0% to 25% acetone in hexanes) to give compound **T53** (167 mg, 75% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.61 (d, J = 4.8 Hz, 1H), 8.20 (dd, J = 0.9, 1.7 Hz, 1H), 8.07 (dd, J = 1.6, 5.2 Hz, 1H), 7.51 (m, 1H), 7.45 (dt, J = 2.0, 7.2 Hz, 1H), 7.34 (br t, J = 7.6 Hz, 1H), 7.21 (br t, J = 9.2 Hz, 1H), 2.82 (m, 2H), 2.62 (qd, J = 6.7, 13.4 Hz, 1H), 2.24 (m, 2H), 2.12 (m, 1H), 1.80 (m, 1H), 1.55 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H), 1.12 (m, 2H), 1.04 (m, 2H); *m/z* = 465 (M+1).

Compound 149: A mixture of compound **88** (3.50 g, 10.16 mmol), thiourea (850 mg, 11.18 mmol) and potassium *t*-butoxide (1.15 g, 10.27 mmol) in EtOH (14 mL) was heated in a Biotage® microwave synthesizer at 120 °C for 1 h. After the reaction mixture was cooled to room temperature, MTBE was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4,

filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **149** (3.25 g, 79% yield) as a white foam. *m/z* = 403 (M+1).

Compound 150: To a solution of compound **149** (5.40 g, 13.42 mmol) in CH_2Cl_2 (135 mL) was added DDQ (4.70 g, 20.70 mmol). After stirring at room temperature for 30 min, the mixture was diluted with MTBE, and washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **150** (3.90 g, 72% yield) as a white foam. *m/z* = 799 (M+1).

Compound 151: To a solution of compound **150** (3.90 g, 4.88 mmol) in THF (12 mL) and EtOH (48 mL) were added iodomethane (3.04 mL, 48.85 mmol) and sodium borohydride (1.50 g, 39.65 mmol) sequentially at 0 °C. After stirring the mixture at room temperature for 1 h, additional amount of sodium borohydride (0.50 g, 13.21 mmol) was added. The mixture was stirred at room temperature for another 45 min, and then partitioned between EtOAc and aq. 10% Na_2SO_3. The organic extract was washed with brine, dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **151** (3.50 g, 86% yield) as a white foam. *m/z* = 415 (M+1).

Compound 152a: A mixture of compound **151** (414 mg, 1.00 mmol), copper(I) thiophene-2-carboxylate (570 mg, 3.00 mmol), 2-(trifluoromethyl)pyridine-4-boronic acid (381 mg, 2.00 mmol) and THF (10 mL) in a pressure bottle was sparged with nitrogen for 5 min. Tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) was added, and the nitrogen sparging was continued for another 2 min. The bottle was sealed, and heated at 100 °C for 14 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with aq. 1 N NaOH and water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give the compound **152a** (273 mg, 53% yield) as a white foamy solid. *m/z* = 514 (M+1).

Compound 153a: Compound **152a** (271 mg, 0.53 mmol) was taken up in THF (1.75 mL) and MeOH (1.75 mL). Aq. 3 N HCl (1.75 mL, 52.5 mmol) was added. The mixture was stirred overnight at room temperature. After concentrated, aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated to give compound **153a** (248 mg, quantitative yield) as a light yellow foamy solid. *m/z* = 470 (M+1).

Compound 154a: Compound **153a** (246 mg, 0.52 mmol) was dissolved in ethyl formate (1.3 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.8 mL, 7.79 mmol) was added. The mixture was stirred at room temperature for 2 h, and cooled to 0 °C. Aq. 6 N HCl (1.3 mL, 7.8 mmol), EtOH (5.2 mL) and hydroxylamine hydrochloride (55 mg, 0.79 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40%

EtOAc in hexanes) to give compound **154a** (140 mg, 54% yield) as a yellow foamy solid. *m/z* = 495 (M+1).

Compound 155a: Compound **154a** (137 mg, 0.28 mmol) was dissolved in MeOH (1.4 mL). Sodium methoxide (25 wt.% in methanol, 96 μL, 0.42 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **155a** (117 mg, 85% yield) as a white foamy solid. *m/z* = 495 (M+1).

T54: Compound **155a** (117 mg, 0.24 mmol) was dissolved in anhydrous DMF (0.8 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (34 mg, 0.12 mmol) in DMF (0.4 mL) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (58 μL, 0.72 mmol) was added. The reaction was heated at 55 °C (oil bath) for 2.5 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **T54** (107 mg, 91% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.92 (d, J = 5.1 Hz, 1H), 8.70 (dd, J = 0.8, 1.2 Hz, 1H), 8.57 (dd, J = 1.5, 5.1 Hz, 1H), 7.54 (m, 1H), 7.45 (dt, J = 1.9, 7.4 Hz, 1H), 7.36 (dt, J = 1.1, 7.5 Hz, 1H), 7.23 (m, 1H), 2.85 (m, 2H), 2.63 (td, J = 6.7, 13.4 Hz, 1H), 2.27 (dt, J = 2.7, 12.8 Hz, 1H), 2.16 (m, 1H), 1.81 (dq, J = 7.1, 13.1 Hz, 1H), 1.55 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H); *m/z* = 493 (M+1).

Compound 152b: A mixture of compound **151** (414.5 mg, 1.00 mmol), copper(I) thiophene-2-carboxylate (570 mg, 2.99 mmol), 3-picoline-4-boronic acid (274 mg, 2.00 mmol) and THF (10 mL) in a pressure bottle was sparged with nitrogen for 5 min. Tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) was added, and the nitrogen sparging was continued for another 2 min. The bottle was sealed, and heated at 100 °C for 14 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with aq. 1 N NaOH and water. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give the compound **152b** (50 mg, 11% yield) as a white foam. *m/z* = 460 (M+1). The starting material compound **151** (340 mg, 82% yield) was also recovered after the flash chromatography.

Compound 153b: To a solution of Compound **152b** (115 mg, 0.25 mmol) in MeOH (0.8 mL) and THF (0.8 mL) was added aq. 3 N HCl (0.8 mL, 2.4 mmol). The reaction mixture was stirred for 4 h at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried over Na_2SO_4, filtered and concentrated to give compound **153b** (100 mg, 96% yield) as a white foam. *m/z* = 416 (M+1).

Compound 154b: Compound **153b** (100 mg, 0.24 mmol) was dissolved in ethyl formate (0.6 mL, 7.46 mmol) and cooled to 0 °C. Sodium methoxide (25 wt.% solution in MeOH, 0.823 mL, 3.56

mmol) was added. The mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. Aq. 6 N HCl (0.6 mL, 3.6 mmol) was added to adjust the reaction mixture to pH ~2. EtOH (4 mL) and hydroxylamine hydrochloride (27 mg, 0.39 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, cooled and concentrated. The residue was partitioned between EtOAc and aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **154b** (54 mg, 51% yield) as a white foam. *m/z* = 441 (M+1).

Compound 155b (T55): To a solution of compound **154b** (54 mg, 0.12 mmol) in MeOH (0.6 mL) was added sodium methoxide (25 wt.% solution in MeOH, 0.07 mL, 0.30 mmol). The reaction mixture was stirred at 55 °C for 2 h, cooled to 0 °C, and then neutralized by adding aq. 10% NaH_2PO_4. MeOH was removed by evaporation. The residue was partitioned between EtOAc and water. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **155b** (24 mg, 44% yield) as a pale yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (m, 2H), 7.87 (m, 1H), 7.47 (m, 2H), 7.30 (dt, J = 1.1, 7.5 Hz, 1H), 7.20 (m, 1H), 3.89 (dd, J = 5.7, 13.8 Hz, 1H), 3.47 (dd, J = 5.7, 13.7 Hz, 1H), 2.80 (m, 2H), 2.63 (s, 3H), 2.60 (m, 1H), 2.26 (t, J = 13.7 Hz, 1H), 2.04 (m, 1H), 1.91 (dt, J = 2.7, 12.5 Hz, 1H), 1.70 (dq, J = 7.6, 13.1 Hz, 1H), 1.54 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H); *m/z* = 441 (M+1).

T56: Compound **155b** (23 mg, 0.052 mmol) was dissolved in dry DMF (0.6 mL) and cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (7.5 mg, 0.026 mmol) in DMF (0.3 mL) was added. After the reaction mixture was stirred at 0 °C for 1 h, pyridine (0.012 mL, 0.15 mmol) was added. The reaction was heated at 55 °C for 3 h, and cooled to room temperature. CH_2Cl_2 (10 mL) was added. The mixture was washed with water (4 × 10 mL). The organic extract was dried with Na_2SO_4, filtered and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene (10 mL). The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **T56** (14 mg, 61% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.60 (m, 2H), 7.88 (d, J = 5.1 Hz, 1H), 7.50 (m, 1H), 7.43 (dt, J = 1.8, 7.4 Hz, 1H), 7.32 (dt, J = 1.1, 7.5 Hz, 1H), 7.21 (m, 1H), 2.83 (m, 2H), 2.65 (s, 3H), 2.61 (m, 1H), 2.27 (dt, J = 2.8, 12.8 Hz, 1H), 2.14 (m, 1H), 1.81 (m, 1H), 1.55 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 439 (M+1).

Compound 152c: A mixture of compound **151** (275 mg, 0.664 mmol), 3-fluoropyridine-4-boronic acid hydrate (214.4 mg, 1.349 mmol), copper(I)-thiophene-2-carboxylate (382.2 mg, 2.004 mmol), tetrakis(triphenylphosphine)palladium(0) (39.3 mg, 0.034 mmol) and THF (5 mL) was sparged with N_2 for 3 min. The tube was sealed and heated to 100 °C for 17 h. The resultant mixture was diluted with EtOAc (10 mL), filtered through a plug of Celite®, and eluted with EtOAc (75 mL) and CH_2Cl_2 (25 mL). The combined eluent was concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 85% EtOAc in hexanes) to give compound **152c** (237 mg, 70% purity) as an off-white solid. *m/z* = 464 (M+1).

Compound 153c: A suspension of impure compound **152c** (237 mg), aq. 3 N HCl (4.8 mL, 14.4 mmol), MeOH (4.8 mL) and THF (2.4 mmol) was stirred at room temperature for 5 h. The mixture was diluted with saturated $NaHCO_3$ (25 mL), and extracted with EtOAc (200 mL, then 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 75% EtOAc in hexanes) to give compound **153c** (175 mg, 63% yield from **151**) as a white foam solid. *m/z* = 420 (M+1).

Compound 154c: A solution of sodium methoxide (25 wt.% in MeOH, 1 mL, 4.37 mmol) was added to a 0 °C solution of compound **153c** (175 mg, 0.417 mmol) in ethyl formate (4 mL, 49.73 mmol). The mixture was stirred at 0 °C for 15 min, warmed to room temperature for an additional 1.5 h. The mixture was cooled to 0 °C; acidified with aq. 6 N HCl (0.73 mL, 4.38 mmol); hydroxylamine hydrochloride (47.3 mg, 0.681 mmol) and EtOH (10 mL) were added and the reaction was heated to 55 °C for 20 h. The mixture was concentrated to 4 mL; diluted with EtOAc (100 mL); washed with aq. sat. $NaHCO_3$ (25 mL) and brine (25 mL); dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 75% EtOAc in hexanes) to give compound **154c** (168.5 mg, 91% yield) as a white foam solid. *m/z* = 445 (M+1).

Compound 155c: A solution of sodium methoxide (25% in MeOH, 0.13 mL, 0.57 mmol) was added to a room temperature mixture of compound **154c** (168 mg, 0.378 mmol) in MeOH (1.9 mL). The mixture was stirred at room temperature for 1.25 h, diluted with aq. 10% NaH_2PO_4 (10 mL), and extracted with MTBE (75 mL) and EtOAc (25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 75% EtOAc in hexanes) to give compound **155c** (150 mg, 89% yield) as a white foam solid. *m/z* = 445 (M+1).

T57: A solution of 1,3-dibromo-5,5-dimethylhydantoin (46.9 mg, 0.164 mmol) in DMF (1.4 mL) was added to a 0 °C solution of compound **155c** (144.5 mg, 0.325 mmol) in DMF (3.6 mL). After 1.5 h, pyridine (0.08 mL, 0.99 mmol) was added and the reaction was heated to 55 °C for 2 h. The mixture was diluted with EtOAc (100 mL); washed with aq. sat. $NaHCO_3$ (25 mL), aq. 10% Na_2SO_3 (10 mL) and brine (10 mL). The organic extract was dried over Na_2SO_4, filtered, concentrated and azeotroped with toluene. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **T57** (98.2 mg, 68% yield) as a white foam solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.65 (d, *J* = 2.9 Hz, 1H), 8.56 (d, *J* = 4.9 Hz, 1H), 8.06 (dd, *J* = 5.0, 6.6 Hz, 1H), 7.51 (m, 1H), 7.44 (dt, J = 2.0, 7.6 Hz, 1H), 7.33 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.21 (ddd, *J* = 1.0, 8.4, 9.6 Hz, 1H), 2.84 (m, 2H), 2.62 (qd, *J* = 6.7, 13.4 Hz, 1H), 2.26 (dt, *J* = 2.8, 12.8 Hz, 1H), 2.13 (m, 1H), 1.81 (m, 1H), 1.54 (s, 3H), 1.32 (d, *J* = 6.7 Hz, 3H); *m/z* = 443 (M+1).

Compound 152d: A mixture of compound **151** (419.4 mg, 1.012 mmol), (3-methyl-5-pyridyl)boronic acid (281 mg, 2.052 mmol), copper(I)-thiophene-2-carboxylate (583 mg, 3.057 mmol), tetrakis(triphenylphosphine)palladium(0) (87.9 mg, 0.0761 mmol) and THF (10 mL) was sparged with nitrogen for 3 min. The tube was sealed and heated to 100 °C for 17 h. After cooled to room temperature, the resultant mixture was filtered through a plug of Celite®, eluted with EtOAc (40 mL),

CH_2Cl_2 (40 mL) and acetone (40 mL); and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 75% EtOAc in hexanes) to give compound **152d** (131.3 mg, 28% yield) as a white solid. *m/z* = 460 (M+1).

Compound 153d: A suspension of compound **152d** (197.5 mg, 0.430), aq. 3 N HCl (5 mL, 15 mmol), MeOH (5 mL) and THF (2.5 mmol) was stirred at room temperature for 5 h. The mixture was diluted with aq. sat. $NaHCO_3$ (25 mL), and extracted with EtOAc (200 ml, then 25 mL). The combined organic fractions were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **153d** (165 mg, 92% yield) as a white solid. *m/z* = 416 (M+1).

Compound 154d: A solution of sodium methoxide (25 wt.% in MeOH, 0.91 mL, 3.98 mmol) was added to a 0 °C solution of compound **153d** (165 mg, 0.395 mmol) in ethyl formate (6 mL, 74.60 mmol). The mixture was stirred at 0 °C for 15 min, warmed to room temperature for an additional 2 h. The mixture was cooled to 0 °C; acidified with aq. 6 N HCl (0.67 mL, 4.02 mmol); hydroxylamine hydrochloride (46.4 mg, 0.668 mmol) and EtOH (10 mL) were added and reaction was heated to 55 °C for 3 h. The mixture was diluted with aq. 10% NaH_2PO_4 (10 mL), and extracted with MTBE (75 mL) and EtOAc (25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give compound **154d** (146.4 mg, 84% yield) as a white solid. *m/z* = 441 (M+1).

Compound 155d: A solution of sodium methoxide (25 wt.% in MeOH, 0.12 mL, 0.53 mmol) was added to a room temperature mixture of compound **154d** (146 mg, 0.332 mmol) in MeOH (1.7 mL). The mixture was stirred at room temperature for 1.5 h, diluted with aq. 10% NaH_2PO_4 (25 mL), and extracted with MTBE (75 mL) and EtOAc (25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 80% EtOAc in hexanes) to give compound **155d** (85.9 mg, 59% yield) as a white foam solid. *m/z* = 441 (M+1).

T58: A solution of 1,3-dibromo-5,5-dimethylhydantoin (27.9 mg, 0.0976 mmol) in DMF (1.0 mL) was added to a 0 °C solution of compound **155d** (85.9 mg, 0.195 mmol) in DMF (2.0 mL). After 2 h, pyridine (0.05 mL, 0.62 mmol) was added and the reaction was heated to 55 °C for 2 h. The mixture was diluted with EtOAc (125 mL); washed with aq. sat. $NaHCO_3$ (25 mL), aq. 10% Na_2SO_3 (25 mL) and brine (25 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 80% EtOAc in hexanes) to give **T58** (64.7 mg, 76% yield) as a white foam solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, *J* = 2.0 Hz, 1H), 9.02 (s, 1H), 8.56 (d, J = 1.6 Hz, 1H), 8.53 (m, 1H), 7.51 (m, 1H), 7.45 (dt, J = 1.2, 7.6 Hz, 1H), 7.33 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.21 (ddd, *J* = 1.0, 8.4, 9.5 Hz, 1H), 2.80 (m, 2H), 2.62 (qd, *J* = 6.7, 13.4 Hz, 1H), 2.47 (s, 3H), 2.26 (dt, *J* = 2.7, 12.7 Hz, 1H), 2.12 (m, 1H), 1.79 (m, 1H), 1.55 (s, 3H), 1.32 (d, *J* = 6.7 Hz, 3H); *m/z* = 439 (M+1).

Compound 152e: A mixture of compound **151** (419.4 mg, 1.012 mmol), 3-quinolineboronic acid (343.6 mg, 1.986 mmol), copper(I)-thiophene-2-carboxylate (571.8 mg, 2.998 mmol), tetrakis(triphenylphosphine)palladium(0) (87.9 mg, 0.0761 mmol) and THF (10 mL) was sparged with N_2

for 2 min. The tube was sealed and heated to 100 °C for 17 h. After cooled to room temperature, the resultant mixture was filtered through a plug of Celite®; eluted with EtOAc (25 mL), CH_2Cl_2 (25 mL) and acetone (25 mL); and concentrated. The resultant material was diluted with EtOAc (150 mL); washed with aq. sat. $NaHCO_3$ (2 × 30 mL) and brine (25 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give compound **152e** (204.4 mg, 41% yield) as an off-white solid. *m/z* = 496 (M+1).

Compound 153e: A suspension of compound **152e** (204.4 mg, 0.412 mmol), aq. 3 N HCl (5 mL, 15.0 mmol), MeOH (5 mL) and THF (2.5 mmol) was stirred at room temperature for 4 h. The mixture was diluted with aq. sat. $NaHCO_3$ (30 mL), and extracted with EtOAc (150 mL, then 50 mL). The combined organic fractions were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **153e** (182.1 mg, 98% yield) as a white foam solid. *m/z* = 452 (M+1).

Compound 154e: A solution of sodium methoxide (25 wt.% in MeOH, 0.92 mL, 4.02 mmol) was added to a 0 °C solution of compound **153e** (182.1 mg, 0.401 mmol) in ethyl formate (6.1 mL, 75.84 mmol). The mixture was stirred at 0 °C for 5 min, warmed to room temperature for an additional 1 h. The mixture was cooled to 0 °C; acidified with aq. 6 N HCl (0.67 mL, 4.02 mmol); hydroxylamine hydrochloride (44.8 mg, 0.645 mmol) and EtOH (10.2 mL) were added and reaction was heated to 55 °C overnight. The mixture was diluted with aq. sat. $NaHCO_3$ (25 mL) and extracted with EtOAc (75 mL, then 25 mL). The combined organic fractions were washed with brine (25 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give compound **154e** (163.2 mg, 85% yield) as a white foam solid. *m/z* = 477 (M+1).

Compound 155e: A solution of sodium methoxide (25 wt.% in MeOH, 0.20 mL, 0.88 mmol) was added to a room temperature mixture of compound **154e** (163 mg, 0.342 mmol) in MeOH (6.8 mL). The mixture was stirred at 55 °C for 2 h, diluted with aq. 10% NaH_2PO_4 (30 mL), and extracted with MTBE (100 mL) and EtOAc (50 mL). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 75% EtOAc in hexanes) to give compound **155e** (126.3 mg, 77% yield) as a white solid. *m/z* = 477 (M+1).

T59: A solution of 1,3-dibromo-5,5-dimethylhydantoin (14.8 mg, 0.0518 mmol) in DMF (1.0 mL) was added to a 0 °C solution of compound **155e** (48.8 mg, 0.102 mmol) in DMF (3.0 mL). After 1 h, pyridine (0.04 mL, 0.50 mmol) was added and the reaction was heated to 55 °C for 2 h. The mixture was diluted with EtOAc (125 mL); washed with aq. sat. $NaHCO_3$ (25 mL), aq. 10% Na_2SO_3 (25 mL) and brine (25 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 75% EtOAc in hexanes) to give **T59** (34.3 mg, 71% yield) as an off-white foam solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (d, *J* = 2.2 Hz, 1H), 9.24 (d, *J* = 1.6 Hz,

1H), 9.09 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.02 (dd, J = 1.4, 8.2 Hz, 1H), 7.79 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 7.62 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 7.52 (m, 2H), 7.36 (dt, J = 1.1, 7.5 Hz, 1H), 7.23 (m, 1H), 2.83 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.29 (dt, J = 2.8, 12.8 Hz, 1H), 2.14 (m, 1H), 1.82 (m, 1H), 1.59 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475.2 (M+1).

Compound 152f: A mixture of compound **151** (418.5 mg, 1.010 mmol), uinolone-6-boronic acid (344.5 mg, 1.992 mmol), copper(I)-thiophene-2-carboxylate (574.7 mg, 3.014 mmol), tetrakis(triphenylphosphine)palladium(0) (86.9 mg, 0.0752 mmol) and THF (10 mL) was sparged with nitrogen for 3 min. The tube was sealed and heated to 100 °C for 21 h. After cooled to room temperature, the resultant mixture was filtered through a plug of Celite®; eluted with EtOAc (40 mL), CH_2Cl_2 (40 mL) and acetone (40 mL); and concentrated. The resultant material was diluted with EtOAc (100 mL); washed with aq. sat. $NaHCO_3$ (2 × 25 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 80% EtOAc in hexanes) to give compound **152f** (155.6 mg, 31% yield) as a white foam solid. *m/z* = 496.2 (M+1).

Compound 153f: A suspension of compound **152f** (156 mg, 0.314 mmol), aq. 3 N HCl (5 mL, 15.0 mmol), MeOH (5 mL) and THF (2.5 mmol) was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (100 mL); washed with aq. sat. $NaHCO_3$ (25 mL) and brine (25 mL); dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give compound **153f** (134.4 mg, 95% yield) as a white foam solid. *m/z* = 452.2 (M+1).

Compound 154f: A solution of sodium methoxide (25 wt.% in MeOH, 0.68 mL, 2.97 mmol) was added to a 0 °C solution of compound **153f** (134.4 mg, 0.296 mmol) in ethyl formate (6.5 mL, 80.82 mmol). The mixture was stirred at 0 °C for 5 min, warmed to room temperature for an additional 2 h. The mixture was cooled to 0 °C; acidified with aq. 6 N HCl (0.50 mL, 3.0 mmol); hydroxylamine hydrochloride (30.9 mg, 0.445 mmol) and EtOH (7.5 mL) were added and reaction was heated to 55 °C overnight. The mixture was diluted with aq. sat. $NaHCO_3$ (50 mL) and extracted with EtOAc (75 mL, then 25 mL). The combined organic fractions were washed with brine (25 mL); dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 75% EtOAc in hexanes) to give compound **154f** (122 mg, 86% yield) as a white foam solid. *m/z* = 477.2 (M+1).

Compound 155f: A solution of sodium methoxide (25 wt.% in MeOH, 0.15 mL, 0.66 mmol) was added to a room temperature mixture of compound **154f** (122 mg, 0.256 mmol) in MeOH (5.1 mL). The mixture was stirred at 55 °C for 2 h, diluted with aq. 10% NaH_2PO_4 (50 mL), and extracted with MTBE (100 mL) and EtOAc (25 mL). The combined organic fractions were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 80% EtOAc in hexanes) to give compound **155f** (51.4 mg, 42% yield) as a white solid. *m/z* = 477.2 (M+1).

T60: A solution of 1,3-dibromo-5,5-dimethylhydantoin (15.8 mg, 0.0553 mmol) in DMF (1.0 mL) was added to a 0 °C solution of compound **155f** (51.4 mg, 0.108 mmol) in DMF (3.0 mL). After 2 h,

pyridine (0.05 mL, 0.62 mmol) was added and the reaction was heated to 55 °C for 2 h. The mixture was diluted with EtOAc (125 mL); washed with aq. sat. $NaHCO_3$ (25 mL), aq. 10% Na_2SO_3 (25 mL), water (25 mL) and brine (25 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give **T60** (34.8 mg, 68% yield) as an off-white foam solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 9.01 (d, J = 1.9 Hz, 1H), 8.98 (dd, J = 1.8, 4.3 Hz, 1H), 8.87 (dd, J = 2.0, 8.9 Hz, 1H), 8.36 (m, 1H), 8.23 (d, J = 8.9 Hz, 1H), 7.50 (m, 3H), 7.35 (dt, J = 1.1, 7.5 Hz, 1H), 7.23 (m, 1H), 2.82 (m, 2H), 2.64 (qd, J = 6.7, 13.3 Hz, 1H), 2.29 (dt, J = 2.7, 12.8 Hz, 1H), 2.13 (m, 1H), 1.81 (m, 1H), 1.59 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475.2 (M+1).

Compound 152g: A mixture of compound **151** (418.6 mg, 1.010 mmol), *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)uinolon-2-yl)acetamide (524.6 mg, 2.001 mmol), copper(I)-thiophene-2-carboxylate (575.6 mg, 3.018 mmol), tetrakis(triphenylphosphine)palladium(0) (89.5 mg, 0.0774 mmol) and THF (10 mL) was sparged with nitrogen for 3 min. The tube was sealed and heated to 100 °C for 18 h. After cooled to room temperature, the resultant mixture was filtered through a plug of Celite®; eluted with EtOAc (25 mL), CH_2Cl_2 (25 mL) and acetone (25 mL); and concentrated. The resultant material was diluted with EtOAc (150 mL); washed with aq. sat. $NaHCO_3$ (2 × 35 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give compound **152g** (74.9 mg, 15% yield) as a glassy solid. *m/z* = 503.2 (M+1).

Compound 153g: A suspension of compound **152g** (74.9 mg, 0.149 mmol), aq. 3 N HCl (2.4 mL, 7.2 mmol), MeOH (2.4 mL) and THF (1.2 mmol) was stirred at room temperature for 4 h, concentrated and loaded directly onto silica, and purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **153g** (40.3 mg, 59% yield) as a white solid. *m/z* = 459.2 (M+1).

Compound 154g: A solution of sodium methoxide (25 wt.% in MeOH, 0.20 mL, 0.87 mmol) was added to a 0 °C solution of compound **153g** (40.3 mg, 0.0879 mmol) in ethyl formate (4 mL, 49.73 mmol). The mixture was stirred at 0 °C for 5 min, warmed to room temperature for an additional 3 h. The mixture was cooled to 0 °C; acidified with aq. 6 N HCl (0.15 mL, 0.90 mmol); hydroxylamine hydrochloride (9.4 mg, 0.135 mmol) and EtOH (2.3 mL) were added and reaction was heated to 55 °C overnight. The mixture was diluted with aq. sat. $NaHCO_3$ (25 mL) and extracted with EtOAc (2 × 50 mL). The combined organic fractions were washed with brine (25 mL); dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **154g** (32.7 mg, 77% yield) as a white solid. *m/z* = 484.2 (M+1).

Compound 155g: A solution of sodium methoxide (25 wt.% in MeOH, 0.04 mL, 0.18 mmol) was added to a room temperature mixture of compound **154g** (32.7 mg, 0.0676 mmol) in MeOH (1.4 mL). The mixture was stirred at 55 °C for 1 h, diluted with aq. 10% NaH_2PO_4 (10 mL), and extracted with MTBE (50 mL) and EtOAc (25 mL). The combined organic fractions were washed with brine (10

mL), dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **155g** (34.7 mg, quantitative yield) which was used as-is in subsequent reaction.

T61: A solution of 1,3-dibromo-5,5-dimethylhydantoin (4.5 mg, 0.016 mmol) in DMF (0.6 mL) was added to a 0 °C solution of compound **155g** (15.1 mg, 0.0312 mmol) in DMF (1.0 mL). After 2 h, pyridine (15 μL, 0.19 mmol) was added and the reaction was heated to 55 °C for 2 h. The mixture was diluted with EtOAc (75 mL); washed with aq. sat. $NaHCO_3$ (10 mL), aq. 10% Na_2SO_3 (10 mL) and brine (10 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give **T61** (9.1 mg, 61% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 9.00 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H), 8.35 (br s, 1H), 8.08 (dd, J = 1.5, 5.2 Hz, 1H), 7.48 (m, 2H), 7.32 (dt, J = 1.1, 7.5 Hz, 1H), 7.19 (ddd, J = 1.0, 8.4, 9.6 Hz, 1H), 2.82 (m, 2H), 2.62 (qd, J = 6.7, 13.4 Hz, 1H), 2.25 (s, 3H), 2.25 (m, 1H), 2.12 (m, 1H), 1.80 (m, 1H), 1.55 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 482.2 (M+1).

Compound 152h: A mixture of compound **151** (424.2 mg, 1.023 mmol), 8-quinolinylboronic acid (230.5 mg, 1.333 mmol), copper(I)-thiophene-2-carboxylate (574 mg, 3.01 mmol), tetrakis(triphenylphosphine)palladium(0) (86.6 mg, 0.0749 mmol) and THF (10 mL) was sparged with nitrogen for 5 min. The tube was sealed and heated to 100 °C overnight. After cooled to room temperature, the resultant mixture was filtered through a plug of Celite®, eluted with EtOAc (40 mL), CH_2Cl_2 (40 mL) and acetone (40 mL); and concentrated. The resultant residue was dissolved in EtOAc (100 mL), washed with aq. sat. $NaHCO_3$ (2 × 25 mL), dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **152h** (75.5 mg, 15% yield) as a white solid. m/z = 496.2 (M+1).

Compound 153h: A suspension of compound **152h** (75.5 mg, 0.152 mmol), aq. 3 N HCl (2 mL, 6 mmol), MeOH (2 mL) and THF (1 mmol) was stirred at room temperature for 3 h. The mixture was diluted with aq. sat. $NaHCO_3$ (10 mL), and extracted with EtOAc (50 ml, then 20 mL). The combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The resultant crude compound **153h** (66.6 mg) was used without further purification.

Compound 154h: A solution of sodium methoxide (25 wt.% in MeOH, 0.34 mL, 1.49 mmol) was added to a 0 °C solution of compound **153h** (66.6 mg, ≤ 0.147 mmol) in ethyl formate (2.2 mL, 27.35 mmol). The mixture was stirred at 0 °C for 5 min, warmed to room temperature for an additional 3 h. The mixture was cooled to 0 °C; acidified with aq. 6 N HCl (0.25 mL, 1.5 mmol); hydroxylamine hydrochloride (18.3 mg, 0.263 mmol) and EtOH (3.7 mL) were added and reaction was heated to 55 °C overnight. The mixture was diluted with aq. 10% NaH_2PO_4 (10 mL), and extracted with MTBE (75 mL) and EtOAc (25 mL). The combined organic fractions were dried over Na_2SO_4, filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **154h** (57.2 mg, 79% yield from compound **152h**) as a white solid. *m/z* = 477.2 (M+1).

Compound 155h: A solution of sodium methoxide (25 wt.% in MeOH, 0.05 mL, 0.22 mmol) was added to a room temperature mixture of compound **154h** (57.2 mg, 0.120 mmol) in MeOH (2 mL). The mixture was stirred at room temperature for 2 h, diluted with EtOAc (100 mL), washed with aq. 10% NaH_2PO_4 (25 mL), dried over Na_2SO_4 , filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **155h** (48.3 mg, 84% yield) as a glassy solid. *m/z* = 477.2 (M+1).

T62: A solution of 1,3-dibromo-5,5-dimethylhydantoin (14.5 mg, 0.0507 mmol) in DMF (1.0 mL) was added to a 0 °C solution of compound **155h** (48.3 mg, 0.101 mmol) in DMF (3.0 mL). After 1 h, pyridine (0.05 mL, 0.62 mmol) was added and the reaction was heated to 55 °C for 3 h. The mixture was diluted with EtOAc (100 mL); washed with aq. sat. $NaHCO_3$ (25 mL), aq. 10% Na_2SO_3 (25 mL) and brine (25 mL); dried over Na_2SO_4; filtered and concentrated. The resultant residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give **T62** (31.5 mg, 65% yield) as a yellow foam solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (dd, *J* = 0.8, 1.2 Hz, 1H), 8.98 (s, 1H), 8.58 (d, *J* = 5.7 Hz, 1H), 8.30 (dd, J = 1.2, 7.2 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.84 (dd, J = 7.2, 8.0 Hz, 1H), 7.74 (dd, *J* = 0.8, 5.5 Hz, 1H), 7.50 (m, 2H), 7.32 (dt, *J* = 1.1, 7.6 Hz, 1H), 7.21 (m, 1H), 2.88 (m, 2H), 2.64 (qd, *J* = 6.8, 13.5 Hz, 1H), 2.31 (dt, J = 2.8, 12.9 Hz, 1H), 2.16 (m, 1H), 1.87 (m, 1H), 1.62 (s, 3H), 1.34 (d, *J* = 6.7 Hz, 3H); *m/z* = 475.2 (M+1).

Compound 157: A mixture of compound **156** (500 mg, 2.56 mmol), bis(pinacolato)diboron (712 mg, 2.80 mmol), potassium acetate (626 mg, 6.38 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (98 mg, 0.013 mmol) and 1,4-dioxane (6 mL) in a vial was sparged with N_2 for 5 min. The vial was sealed, and heated at 125 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc and water. The organic phase of the filtrate was separated, washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **157** (475 mg, 64% yield) as a white solid. *m/z* = 206 (M-C_6H_9).

Compound 158: A mixture of compound **151** (231 mg, 0.56 mmol), copper(I) thiophene-2-carboxylate (320 mg, 1.68 mmol), compound **157** (200 mg, 0.70 mmol) and THF (5 mL) in a pressure bottle was sparged with N_2 for 5 min. Tetrakis(triphenylphosphine)palladium(0) (32 mg, 0.028 mmol) was added. The N_2 sparging was continued for another 2 min. The bottle was sealed, and heated at 100 °C for 14 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with aq. 1 N NaOH and water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give the compound **158** (65 mg, 22% yield) as a white foamy solid. *m/z* = 528 (M+1).

Compound 159: Compound **158** (64 mg, 0.12 mmol) was taken up in MeOH (0.8 mL). Aq. 3 N HCl (0.4 mL, 1.2 mmol) was added. The mixture was stirred for 4 h at room temperature. After concentrated, aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract

was dried with Na_2SO_4, and concentrated to give compound **159** (60 mg, quantitative yield) as a light yellow foamy solid. *m/z* = 484 (M+1).

Compound 160: Compound **159** (57 mg, 0.12 mmol) was dissolved in ethyl formate (0.28 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 0.41 mL, 1.77 mmol) was added. The mixture was stirred at room temperature for 2 h, and cooled to 0 °C. Aq. 6 N HCl (0.3 mL, 1.8 mmol), EtOH (1.2 mL) and hydroxylamine hydrochloride (13 mg, 0.18 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 6 h, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **160** (46 mg, 77% yield) as a white foamy solid. *m/z* = 509 (M+1).

Compound 161: Compound **160** (46 mg, 0.090 mmol) was dissolved in MeOH (0.9 mL). Potassium carbonate (38 mg, 0.28 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **161** (39 mg, 85% yield) as a white foamy solid. *m/z* = 509 (M+1).

T63: Compound **161** (39 mg, 0.077 mmol) was dissolved in benzene (1 mL). DDQ (20 mg, 0.088 mmol) was added. The mixture was heated at 85 °C for 1 h, and cooled to rt. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was stirred for 5 min, and extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **T63** (15 mg, 38% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.38 (td, J = 1.1, 8.5 Hz, 1H), 7.94 (s, 1H), 7.47 (m, 4H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.24 (m, 1H), 2.90 (s, 3H), 2.88 (m, 2H), 2.64 (qd, J = 6.7, 13.3 Hz, 1H), 2.31 (dt, J = 2.8, 12.8 Hz, 1H), 2.17 (m, 1H), 1.87 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 507 (M+1).

Compound 162: A mixture of compound **144** (161 mg, 0.33 mmol), morpholine (59 μL, 0.68 mmol), Xphos (19 mg, 0.040 mmol), tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.013 mmol), sodium *tert*-butoxide (48 mg, 0.50 mmol) and toluene (1 mL) in a vail was sparged with nitrogen for 5 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 100 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give the compound **162** (125 mg, 70% yield) as a light brown foamy solid. m/z = 531 (M+1).

Compound 163: Compound **162** (439 mg, 0.83 mmol) was taken up in THF (2.8 mL) and MeOH (2.8 mL). Aq. 3 N HCl (2.8 mL, 8.4 mmol) was added. The mixture was stirred overnight at room temperature. After concentrated, aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated to give compound **163** (387 mg, 96% yield) as a light brown foamy solid. *m/z* = 487 (M+1).

Compound 164: Compound **163** (385 mg, 0.79 mmol) was dissolved in ethyl formate (1.9 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 2.7 mL, 11.7 mmol) was added. The mixture was stirred at room temperature for 2 h, and cooled to 0 °C. Aq. 6 N HCl (2.0 mL, 12.0 mmol), EtOH (11.9 mL) and hydroxylamine hydrochloride (84 mg, 1.21 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **164** (309 mg, 76% yield) as a yellow foamy solid. *m/z* = 512 (M+1).

Compound 165: Compound **164** (306 mg, 0.60 mmol) was dissolved in MeOH (3 mL). Sodium methoxide (25 wt.% in methanol, 0.21 mL, 0.90 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **165** (273 mg, 89% yield) as a yellow foamy solid. *m/z* = 512 (M+1).

T64: Compound **165** (128 mg, 0.25 mmol) was dissolved in benzene (2.5 mL). DDQ (60 mg, 0.26 mmol) was added. The mixture was heated at reflux for 1 h, and cooled to rt. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was extracted with CH_2Cl_2. The combined organic extract was washed with water and brine, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% EtOAc in CH_2Cl_2) to give compound **T64** (98 mg, 77% yield) as a yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.37 (dd, J = 0.7, 5.3 Hz, 1H), 7.72 (dd, J = 1.2, 5.2 Hz, 1H), 7.69 (t, J = 0.8 Hz, 1H), 7.51 (m, 1H), 7.44 (dt, J = 1.9, 7.4 Hz, 1H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.21 (ddd, J = 1.0, 8.3, 9.6 Hz, 1H), 3.86 (dd, J = 4.0, 5.8 Hz, 4H), 3.62 (dd, J = 3.8, 6.0 Hz, 4H), 2.80 (m, 2H), 2.62 (qd, J = 6.7, 13.4 Hz, 1H), 2.25 (dt, J = 2.7, 12.8 Hz, 1H), 2.11 (m, 1H), 1.79 (dq, J = 7.1, 12.9 Hz, 1H), 1.54 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 510 (M+1).

Compound 166: A mixture of compound **144** (166 mg, 0.35 mmol), phenylboronic acid (55 mg, 0.45 mmol), potassium carbonate (239 mg, 1.73 mmol), toluene (2 mL), EtOH (1 mL) and water (1 mL) in a vail was sparged with nitrogen for 5 min. Tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.010 mmol) was added. The nitrogen sparging was continued for another 2 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 100 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give the compound **166** (180 mg, quantitative yield) as a white foamy solid. *m/z* = 522 (M+1).

Compound 167: Compound **166** (210 mg, 0.40 mmol) was taken up in THF (1.4 mL) and MeOH (1.4 mL). Aq. 3 N HCl (1.4 mL, 8.4 mmol) was added. The mixture was stirred overnight at room temperature. After concentrated, aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc.

The organic extract was dried with Na_2SO_4, and concentrated to give compound **167** (189 mg, 98% yield) as a yellow foamy solid. *m/z* = 478 (M+1).

Compound 168: Compound **167** (187 mg, 0.39 mmol) was dissolved in ethyl formate (945 μL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.4 mL, 6.06 mmol) was added. The mixture was stirred at room temperature for 2 h, and cooled to 0 °C. Aq. 6 N HCl (0.98 mL, 5.88 mmol), EtOH (4 mL) and hydroxylamine hydrochloride (42 mg, 0.60 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give compound **168** (132 mg, 67% yield) as a yellow foamy solid. *m/z* = 503 (M+1).

Compound 169: Compound **168** (130 mg, 0.26 mmol) was dissolved in MeOH (1.3 mL). Sodium methoxide (25 wt.% in methanol, 90 μL, 0.39 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **169** (112 mg, 86% yield) as a white foamy solid. *m/z* = 503 (M+1).

T65: Compound **169** (82 mg, 0.16 mmol) was dissolved in anhydrous DMF (0.4 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (23 mg, 0.080 mmol) in DMF (0.4 mL) was added. The reaction was stirred at 0 °C for 2 h. Pyridine (40 μL, 0.50 mmol) was added. The reaction was heated at 55 °C (oil bath) for 3 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **T65** (63 mg, 76% yield) as a white foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.88 (dd, J = 0.8, 5.1 Hz, 1H), 8.76 (dd, J = 0.9, 1.5 Hz, 1H), 8.30 (dd, J = 1.6, 5.1 Hz, 1H), 8.11 (m, 2H), 7.50 (m, 5H), 7.35 (dt, J = 1.1, 7.5 Hz, 1H), 7.23 (m, 1H), 2.83 (m, 2H), 2.63 (td, J = 6.7, 13.3 Hz, 1H), 2.28 (dt, J = 2.7, 12.8 Hz, 1H), 2.14 (m, 1H), 1.81 (m, 1H), 1.58 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 501 (M+1).

Compound 170a: A mixture of compound **88** (1.30 g, 3.77 mmol), 4-isoquinolinecarboximidamide hydrochloride (1.21 g, 5.81 mmol) and potassium carbonate (1.56 g, 11.28 mmol) in EtOH (38 mL) was refluxed under nitrogen overnight. The mixture was cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved in CH_2Cl_2 (50 mL), and treated with manganese dioxide (88%, 1.63 g, 16.50 mmol). After stirring at room temperature overnight, the mixture was filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **170a** (0.70 g, 38% yield) as a light yellow foamy solid. *m/z* = 496 (M+1).

Compound 171a: A solution of compound **170a** (0.70 g, 1.42 mmol) and aq. 3 N HCl (4.7 mL, 14.1 mmol) in MeOH (15 mL) was stirred at room temperature overnight. The mixture was concentrated, cooled, basified with aq. 10% NH_4OH, and then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **171a** (0.63 g, 98% yield) as an off-white foamy solid. *m/z* = 452 (M+1).

Compound 172a: To a stirring solution at room temperature of compound 171a (0.63 g, 1.40 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.80 mL, 4.26 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **172a** (0.60 g, 88% yield) as a light brown foamy solid. *m/z* = 480 (M+1).

Compound 173a: To a solution of compound **172a** (0.60 g, 1.25 mmol) in EtOH (25 mL) was added acetic acid (0.70 mL, 12.23 mmol) and hydroxylamine hydrochloride (0.13 g, 1.87 mmol). The mixture was heated at 60 °C under nitrogen for 2 h, stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **173a** (0.57 g, 96% yield) as a tan foamy solid. *m/z* = 477 (M+1).

Compound 174a: A mixture of compound **173a** (0.57 g, 1.20 mmol) and potassium carbonate (0.83 g, 6.00 mmol) in MeOH (12 mL) was stirred at room temperature under nitrogen for 16 h. The mixture was filtered, and the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **174a** (0.37 g, 65% yield) as a light yellow foamy solid. *m/z* = 477 (M+1).

T66: To a stirring solution at 0 °C under nitrogen of compound **174a** (0.37 g, 0.78 mmol) in degassed DMF (8 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.12 g, 0.42 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (0.6 mL, 7.44 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 70% EtOAc in hexanes) to give compound **T66** (0.13 g, 35% yield) as a light yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 9.22 (s, 1H), 8.98 (s, 1H), 8.79 (ddd, J = 0.8, 1.6, 8.8 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.81 (ddd, J = 1.4, 6.9, 8.6 Hz, 1H), 7.68 (ddd, J = 1.1, 6.9, 8.1 Hz, 1H), 7.50 (m, 2H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.23 (m, 1H), 2.88 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.8, 12.8 Hz, 1H), 2.17 (m, 1H), 1.86 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H); *m/z* = 475 (M+1).

Compound 170b: A mixture of compound **88** (1.30 g, 3.77 mmol), impure pyrazolo[1,5-*a*]pyridine-3-carboximidamide hydrochloride (< 5.78 mmol) and potassium carbonate (1.56 g, 11.28

mmol) in EtOH (38 mL) was refluxed under nitrogen overnight. The mixture was cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved in CH_2Cl_2 (50 mL), and treated with manganese dioxide (88%, 1.7 g, 17.2 mmol). After stirring at room temperature overnight, the mixture was filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **170b** (0.15 g, 8% yield) as a tan foamy solid. *m/z* = 485 (M+1).

Compound 171b: A solution of compound **170b** (0.15 g, 0.31 mmol) and aq. 3 N HCl (1.0 mL, 3.0 mmol) in MeOH (1 mL) was stirred at room temperature overnight. The mixture was concentrated, cooled, basified with aq. 10% NH_4OH, and then extracted with $CHCl_3$ (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **171b** (0.13 g, 96% yield) as a tan foamy solid. *m/z* = 441 (M+1).

Compound 172b: To a stirring solution at room temperature of compound **171b** (0.13 g, 0.30 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.28 mL, 1.49 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (25 mL) and aq. sat. KH_2PO_4 (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **172b** (0.11 g, 80% yield) as a tan foamy solid. *m/z* = 469 (M+1).

Compound 173b: To a solution of compound **172b** (0.11 g, 0.23 mmol) in EtOH (10 mL) was added acetic acid (0.15 mL, 2.62 mmol) and hydroxylamine hydrochloride (0.025 g, 0.36 mmol). The mixture was heated at 60 °C under nitrogen for 2 h, stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give compound **173b** (0.10 g, 91% yield) as a tan foamy solid. *m/z* = 466 (M+1).

Compound 174b: A mixture of compound **173b** (0.10 g, 0.21 mmol) and potassium carbonate (0.15 g, 1.08 mmol) in MeOH (10 mL) was stirred at room temperature under nitrogen for 16 h. After filtration, the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 70% EtOAc in hexanes) to give compound **174b** (0.073 g, 73% yield) as a tan foamy solid. *m/z* = 466 (M+1).

T67: To a stirring solution at 0 °C under nitrogen of compound **174b** (0.073 g, 0.16 mmol) in degassed DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.025 g, 0.087 mmol) in DMF (1 mL). After stirring the mixture for 30 min, pyridine (0.13 mL, 1.61 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was

purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T67** (0.031 g, 42% yield) as a yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.79 (s, 1H), 8.56 (td, J = 1.1, 6.9 Hz, 1H), 8.50 (td, J = 1.3, 9.0 Hz, 1H), 7.49 (m, 2H), 7.35 (m, 2H), 7.21 (ddd, J = 1.0, 8.3, 9.5 Hz, 1H), 6.92 (dt, J = 1.4, 6.9 Hz, 1H), 2.76 (m, 2H), 2.62 (qd, J = 6.7, 13.4 Hz, 1H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.08 (m, 1H), 1.77 (tdd, J = 7.0, 13.0, 19.3 Hz, 1H), 1.57 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 464 (M+1).

Compound 170c: A mixture of compound **88** (1.50 g, 4.36 mmol), 8-methyl-4-quinolinecarboximidamide hydrochloride (1.21 g, 5.46 mmol) and potassium carbonate (1.81 g, 13.10 mmol) in EtOH (30 mL) was refluxed under nitrogen overnight. The mixture was cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved in CH_2Cl_2 (100 mL), treated with manganese dioxide (88%, 2.0 g, 20.2 mmol) and stirred at room temperature overnight. After filtration, the filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give compound **170c** (1.49 g, 67% yield) as light a yellow foamy solid. *m/z* = 510 (M+1).

Compound 171c: A solution of compound **170c** (1.49 g, 2.92 mmol) and aq. 3 N HCl (10 mL, 30 mmol) in MeOH (30 mL) was stirred at room temperature overnight. After concentration, the mixture was cooled, basified with aq. 10% NH_4OH, and then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **171c** (1.44 g, quantitative yield) as a light yellow foamy solid. *m/z* = 466 (M+1).

Compound 172c: To a stirring solution at room temperature of compound **171c** (all from the last step) in ethyl formate (12 mL, 148 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 1.6 mL, 8.64 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **172c** (1.34 g, 92% yield) as a tan foamy solid. *m/z* = 494 (M+1).

Compound 173c: To a solution of compound **172c** (1.34 g, 2.71 mmol) in EtOH (25 mL) was added acetic acid (1.6 mL, 27.9 mmol) and hydroxylamine hydrochloride (0.28 g, 4.03 mmol). The mixture was heated at 60 °C under nitrogen for 2 h, stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **173c** (1.31 g, 98% yield) as a tan foamy solid. *m/z* = 491 (M+1).

Compound 174c: A mixture of compound **173c** (1.31 g, 2.67 mmol) and potassium carbonate (1.84 g, 13.31 mmol) in MeOH (27 mL) was stirred at room temperature under nitrogen for 16 h. After filtration, the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, eluting

with 50% EtOAc in hexanes) to give compound **174c** (0.94 g, 72% yield) as a light yellow foamy solid. *m/z* = 491 (M+1).

T68: To a stirring solution at 0 °C under nitrogen of compound **174c** (0.94 g, 1.91 mmol) in degassed DMF (10 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.30 g, 1.05 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (1.5 mL, 18.5 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T68** (0.30 g, 32% yield) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 4.5 Hz, 1H), 8.94 (s, 1H), 8.48 (m, 1H), 7.97 (d, J = 4.4 Hz, 1H), 7.63 (td, J = 1.3, 7.0 Hz, 1H), 7.49 (m, 3H), 7.32 (dt, J = 1.1, 7.6 Hz, 1H), 7.23 (m, 1H), 2.89 (m, 2H), 2.88 (s, 3H), 2.63 (td, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.17 (m, 1H), 1.85 (m, 1H), 1.59 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 489 (M+1).

Compound 170d: A mixture of compound **1** (1.50 g, 4.36 mmol), 2-methyl-4-quinolinecarboximidamide hydrochloride (1.21 g, 5.46 mmol) and potassium carbonate (1.81 g, 13.10 mmol) in EtOH (30 mL) was refluxed under nitrogen overnight. The mixture was cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved into CH_2Cl_2 (100 mL), and treated with manganese dioxide (88%, 2.0 g, 20.2 mmol). The mixture was stirred at room temperature overnight, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **170d** (1.44 g, 65% yield) as a light yellow foamy solid. *m/z* = 510 (M+1).

Compound 171d: A solution of compound **170d** (1.44 g, 2.83 mmol) and aq. 3 N HCl (9.5 mL, 28.5 mmol) in MeOH (28 mL) was stirred at room temperature overnight, and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **171d** (1.41 g, quantitative yield) as a light yellow foamy solid. *m/z* = 466 (M+1).

Compound 172d: To a stirring solution at room temperature of compound **171d** (all from the last step) in ethyl formate (12 mL, 148 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 1.6 mL, 8.64 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **172d** (1.34 g, 95% yield) as a dark yellow foamy solid. *m/z* = 494 (M+1).

Compound 173d: To a solution of compound **172d** (1.34 g, 2.71 mmol) in EtOH (25 mL) was added acetic acid (1.6 mL, 27.9 mmol) and hydroxylamine hydrochloride (0.28 g, 4.03 mmol). The mixture was heated at 60 °C under nitrogen for 2 h, stirred at room temperature overnight, concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract

was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **173d** (1.28 g, 96% yield) as an orange foamy solid. *m/z* = 491 (M+1).

Compound 174d: A mixture of compound **173d** (1.28 g, 2.62 mmol) and potassium carbonate (1.81 g, 13.10 mmol) in MeOH (26 mL) was stirred at room temperature under nitrogen for 16 h. The mixture was filtered, and the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **174d** (0.80 g, 63% yield) as a light yellow foamy solid. *m/z* = 491 (M+1).

T69: To a stirring solution at 0 °C under nitrogen of compound **174d** (0.80 g, 1.64 mmol) in degassed DMF (8 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.26 g, 0.91 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (1.3 mL, 16.1 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes), and then crystallized from EtOH to give compound **T69** (0.14 g, 18% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.57 (dd, J = 1.4, 8.6 Hz, 1H), 8.12 (ddd, J = 0.8, 1.2, 8.4 Hz, 1H), 7.86 (s, 1H), 7.73 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H), 7.52 (m, 3H), 7.33 (dt, J = 1.0, 7.5 Hz, 1H), 7.23 (m, 1H), 2.88 (m, 2H), 2.85 (s, 3H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.17 (m, 1H), 1.86 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 489 (M+1).

Compound 170e: A mixture of compound **88** (1.51 g, 4.38 mmol), impure 2,4-dimethyl-5-thiazolecarboximidamide hydrochloride (< 6.58 mmol) and potassium carbonate (3.0 g, 21.7 mmol) in EtOH (44 mL) was refluxed under nitrogen overnight. The mixture was cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved into CH_2Cl_2 (100 mL), and treated with manganese dioxide (88%, 2.0 g, 20.2 mmol). The mixture was stirred at room temperature overnight, and filtered. The filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give compound **170e** (1.12 g, 53% yield) as a light yellow solid. *m/z* = 480 (M+1).

Compound 171e: A solution of compound **170e** (1.12 g, 2.33 mmol) and aq. 3 N HCl (8 mL, 24 mmol) in MeOH (23 mL) was stirred at room temperature overnight, and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **171e** (1.01 g, quantitative yield) as a light yellow foamy solid. *m/z* = 436 (M+1).

Compound 172e: To a stirring solution at room temperature of compound **171e** (1.01 g, 2.33 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 1.3 mL, 7.02 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (50 mL) and

aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **172e** (1.11 g, quantitative yield) as a dark yellow foamy solid. *m/z* = 464 (M+1).

Compound 173e: To a solution of compound **172e** (all from the last step) in EtOH (25 mL) was added acetic acid (1.4 mL, 24.4 mmol) and hydroxylamine hydrochloride (0.25 g, 3.60 mmol). The mixture was heated at 60 °C under nitrogen for 2 h, stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **173e** (1.08 g, quantitative yield) as a brown foamy solid. *m/z* = 461 (M+1).

Compound 174e. A mixture of compound **173e** (1.08 g, 2.33 mmol) and potassium carbonate (1.62 g, 11.72 mmol) in MeOH (25 mL) was stirred at room temperature under nitrogen for 16 h. The mixture was filtered, and the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **174e** (0.72 g, 67% yield) as a light yellow foamy solid. *m/z* = 461 (M+1).

T70: To a stirring solution at 0 °C under nitrogen of compound **174e** (0.72 g, 1.57 mmol) in degassed DMF (8 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.25 g, 0.87 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (1.3 mL, 16.1 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography repeatedly (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T70** (0.21g, 29% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.49 (m, 1H), 7.41 (dt, J = 1.2, 7.6 Hz, 1H), 7.30 (dt, J = 1.1, 7.5 Hz, 1H), 7.19 (ddd, J = 1.0, 8.4, 9.6 Hz, 1H), 2.86 (s, 3H), 2.75 (m, 2H), 2.70 (s, 3H), 2.59 (qd, J = 6.7, 13.4 Hz, 1H), 2.22 (dt, J = 2.3, 12.8 Hz, 1H), 2.09 (m, 1H), 1.75 (dq, J = 7.1, 13.0 Hz, 1H), 1.50 (s, 3H), 1.31 (d, J = 6.7 Hz, 3H); *m/z* = 459 (M+1).

Compound 170f: A mixture of compound **88** (1.45 g, 4.21 mmol), 5-methyl-1,2,4-oxadiazole-3-carboximidamide hydrochloride (0.86 g, 5.29 mmol) and potassium carbonate (1.74 g, 12.59 mmol) in EtOH (30 mL) was refluxed under nitrogen overnight. The mixture was cooled and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved in CH_2Cl_2 (100 mL), and treated with manganese dioxide (88%, 2.0 g, 20.2 mmol). The mixture was stirred at room temperature overnight, and filtered. The filtrate was concentrated, and the crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **170f** (0.64 g, 34% yield) as an off-white solid. *m/z* = 451 (M+1).

Compound 171f: A solution of compound **170f** (0.64 g, 1.42 mmol) and aq. 3 N HCl (5 mL, 15 mmol) in MeOH (14 mL) was stirred at room temperature overnight, and concentrated. The residue was cooled, basified with aq.10% NH_4OH, and then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **171f** (0.62 g, quantitative yield) as a light yellow foamy solid. *m/z* = 407 (M+1).

Compound 172f: To a stirring solution at room temperature of compound **171f** (all from the last step) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.8 mL, 4.32 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **172f** (0.63 g, quantitative yield) as a bright yellow foamy solid. *m/z* = 435 (M+1).

Compound 173f: To a solution of compound **172f** (all from the last step) in EtOH (20 mL) was added acetic acid (0.8 mL, 14.1 mmol) and hydroxylamine hydrochloride (0.15 g, 2.16 mmol). The mixture was heated at 60 °C under nitrogen for 2 h, stirred at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **173f** (0.33 g, 55% yield) as a yellow foamy solid. *m/z* = 432 (M+1).

Compound 174f: A mixture of compound **173f** (0.33 g, 0.76 mmol) and potassium carbonate (0.32 g, 2.32 mmol) in MeOH (20 mL) was stirred at room temperature under nitrogen for 16 h. The mixture was filtered, and the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes, and then 5% MeOH in $CHCl_3$) to give compound **174f** (0.080 g, 24% yield) as a light yellow foamy solid. *m/z* = 432 (M+1).

T71: To a stirring solution at 0 °C under nitrogen of compound **174f** (0.080 g, 0.18 mmol) in degassed DMF (2 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (0.029 g, 0.10 mmol). After stirring the mixture for 30 min, pyridine (0.15 mL, 1.85 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes) to give compound **T71** (0.045 g, 56% yield) as a light yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.47 (m, 2H), 7.29 (dt, J = 1.2, 7.7 Hz, 1H), 7.17 (dd, J = 8.5, 9.9 Hz, 1H), 2.86 (m, 2H), 2.75 (s, 3H), 2.61 (qd, J = 6.7, 13.3 Hz, 1H), 2.26 (m, 1H), 2.14 (m, 1H), 1.83 (m, 1H), 1.57 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 430 (M+1).

Compound 170g: Compound **88** (850 mg, 2.45 mmol) was taken up in EtOH (20 mL). 1-Methyl-1H-pyrrolo[2,3-b]pyridine-3-carboximidamide hydrochloride (2.1 g, 10 mmol) and potassium carbonate (2.8 g, 20.2 mmol) were added. The reaction mixture was heated at reflux for 16 h, cooled and

concentrated. Water (50 mL) was added. The mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give the dihydropyrimidine. The crude product was taken up in CH_2Cl_2 (20 mL), and treated with manganese dioxide (88%, 1.3 g, 13.3 mmol). The mixture was stirred overnight at room temperature, and filtered. The filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **170g** (1.05 g, 84% yield) as a foam. *m/z* = 499 (M+1).

Compound 171g: Compound **170g** (1.05 g, 2.11 mmol) was taken up in THF (10 mL), and aq. 3 N HCl (5 mL, 15 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, filtered, and concentrated to give compound **171g** (0.95 g, 99% yield) as a foam. *m/z* = 455 (M+1).

Compound 172g: Compound **171g** (0.95 g, 2.09 mmol) was taken up in ethyl formate (15 mL, 186 mmol). Sodium methoxide (30 wt.% in MeOH, 0.75 g, 4.17 mmol) was added. After stirring for 2 h at room temperature, the mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **172g** (0.96 g, 95% yield) as a foam. *m/z* = 483 (M+1).

Compound 173g: Compound **172g** (0.96 g, 1.99 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (1.4 g, 20 mmol) and acetic acid (1.2 g, 20 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **173g** (0.83 g, 87% yield) as a foam. *m/z* = 480 (M+1).

Compound 174g: Compound **173g** (830 mg, 1.73 mmol) was dissolved in MeOH (10 mL). K_2CO_3 (1.2 g, 8.68 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **174g** (410 mg, 49 % yield) as a foam. *m/z* = 480 (M+1).

T72: Compound **174g** (410 mg, 0.85 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (135 mg, 0.47 mmol) in DMF (1 mL) was added. After stirring the mixture at 0 °C for 2 h, pyridine (3 mL, 37.2 mmol) was added. The mixture was heated at 60 °C for 4 h, cooled to room temperature, and partitioned between aq. $NaHCO_3$ and EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T72** (105 mg, 26% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.78 (dd, J = 1.7, 7.9 Hz, 1H), 8.41 (dd, J = 1.6, 4.7 Hz, 1H), 8.25 (s, 1H), 7.50 (m, 2H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.22 (m, 2H), 4.00 (s, 3H), 2.75 (m, 2H), 2.62 (qd, J = 6.7, 13.4 Hz, 1H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.08 (m, 1H), 1.77 (m, 1H), 1.57 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 478 (M+1).

Compound 170h: Compound **88** (1 g, 2.90 mmol) was taken up in EtOH (20 mL). 6-Methylquinoline-4-carboximidamide hydrochloride (820 mg, 3.70 mmol) and potassium carbonate (1.1 g, 7.96 mmol) were added. The reaction mixture was heated at reflux for 16 h, cooled and concentrated. Water (50 mL) was added. The mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give the dihydropyrimidine. The crude product was taken up in CH_2Cl_2 (20 mL), and treated with manganese dioxide (88%, 1.35 g, 13.66 mmol). The mixture was stirred overnight at room temperature, and filtered. The filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **170h** (660 mg, 45% yield) as a foam. *m/z* = 510 (M+1).

Compound 171h: Compound **170h** (660 mg, 1.30 mmol) was taken up in THF (10 mL), and aq. 3 N HCl (5 mL, 15 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, filtered, and concentrated to give compound **171h** (0.61 g, quantitative yield) as a foam. *m/z* = 466 (M+1).

Compound 172h: Compound **171h** (0.61 g, 1.30 mmol) was taken up in ethyl formate (15 mL, 186 mmol). Sodium methoxide (30 wt.% in MeOH, 0.47 g, 2.61 mmol) was added. After stirring for 2 h at room temperature, the mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **172h** (0.59 g, 92% yield) as a foam. *m/z* = 494 (M+1).

Compound 173h Compound **172h** (0.59 g, 1.20 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (0.83 g, 11.94 mmol) and acetic acid (0.72 g, 12 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **173h** (0.57 g, 97% yield) as a foam. *m/z* = 491 (M+1).

Compound 174h Compound **173h** (570 mg, 1.16 mmol) was dissolved in MeOH (10 mL). potassium carbonate (0.8 g, 5.79 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **174h** (400 mg, 70 % yield) as a foam. *m/z* = 491 (M+1).

T73: Compound **174h** (400 mg, 0.82 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (130 mg, 0.45 mmol) in DMF (1 mL) was added. After stirring the mixture at 0 °C for 2 h, pyridine (3 mL, 37.2 mmol) was added. The mixture was heated at 60 °C for 4 h, cooled to room temperature, and partitioned between aq. $NaHCO_3$ and EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T73** (250 mg, 62 % yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 4.5 Hz, 1H), 8.99 (s, 1H), 8.49 (m, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 4.5 Hz, 1H), 7.61 (dd, J = 2.0, 8.6 Hz, 1H), 7.50 (m,

2H), 7.33 (dt, J = 1.1, 7.6 Hz, 1H), 7.23 (m, 1H), 2.91 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.58 (s, 3H), 2.33 (dt, J = 2.7, 12.8 Hz, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 489 (M+1).

Compound 170i: Compound **88** (0.7 g, 2.03 mmol) was taken up in EtOH (20 mL). 4-Quinazolinecarboximidamide hydrochloride (1.6 g, 7.67 mmol) and potassium carbonate (2.1 g, 15.19 mmol) were added. The reaction mixture was heated at reflux for 16 h, cooled and concentrated. Water (50 mL) was added. The mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give the dihydropyrimidine. The crude product was taken up in CH_2Cl_2 (20 mL), and treated with manganese dioxide (88%, 2.0 g, 20.24 mmol). The mixture was stirred overnight at room temperature, and filtered. The filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **170i** (130 mg, 13% yield) as a foam. *m/z* = 497 (M+1).

Compound 171i: Compound **170i** (130 mg, 0.26 mmol) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, filtered, and concentrated to give compound **171i** (120 mg, quantitative yield) as a foam. *m/z* = 453 (M+1).

Compound 172i: Compound **171i** (0.12 g, 0.26 mmol) was taken up in ethyl formate (10 mL, 124 mmol). Sodium methoxide (30 wt.% in MeOH, 0.10 g, 0.56 mmol) was added. After stirring for 2 h at room temperature, the mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **172i** (0.12 g, 94% yield) as a foam. *m/z* = 481 (M+1).

Compound 173i: Compound **172i** (0.12 g, 0.25 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (175 mg, 2.52 mmol) and acetic acid (150 mg, 2.50 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **173i** (0.11 g, 92 % yield) as a foam. *m/z* = 478 (M+1).

Compound 174i: Compound **173i** (110 mg, 0.23 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (160 mg, 1.15 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **174i** (60 mg, 55 % yield) as a foam. *m/z* = 478 (M+1).

T74: Compound **174i** (60 mg, 0.13 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (20 mg, 0.070 mmol) in DMF (1 mL) was added. After stirring the mixture at 0 °C for 2 h, pyridine (1 mL, 12.4 mmol) was added. The mixture was heated at 60 °C for 4 h, cooled to room temperature, and partitioned between aq. $NaHCO_3$ and EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated. The residue was purified

by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T74** (20 mg, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.91 (s, 1H), 8.40 (ddd, J = 0.8, 1.6, 8.3 Hz, 1H), 8.18 (td, J = 0.8, 8.6 Hz, 1H), 7.98 (ddd, J = 1.4, 6.9, 8.5 Hz, 1H), 7.72 (ddd, J = 1.3, 6.9, 8.3 Hz, 1H), 7.49 (m, 2H), 7.31 (dt, J = 1.1, 7.5 Hz, 1H), 7.21 (m, 1H), 2.94 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.32 (dt, J = 2.8, 12.8 Hz, 1H), 2.18 (tdd, J = 3.0, 6.2, 13.8 Hz, 1H), 1.87 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 476 (M+1).

Compound 170j: Compound **88** (0.65 g, 1.88 mmol) was taken up in EtOH (20 mL). 1-Isoquinolinecarboximidamide hydrochloride (790 mg, 3.80 mmol) and potassium carbonate (1.2 g, 8.68 mmol) were added. The reaction mixture was heated at reflux for 16 h, cooled and concentrated. Water (50 mL) was added. The mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$ and concentrated to give the dihydropyrimidine. The crude product was taken up in CH_2Cl_2 (20 mL), and treated with manganese dioxide (88%, 1.1 g, 11.14 mmol). The mixture was stirred overnight at room temperature, and filtered. The filtrate was concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **170j** (190 mg, 20 % yield) as a foam. *m/z* = 496 (M+1).

Compound 171j: Compound **170j** (190 mg, 0.38 mmol) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, then dried with $MgSO_4$, filtered, and concentrated to give compound **171j** (175 mg, quantitative yield) as a foam. *m/z* = 452 (M+1).

Compound 172j: Compound **171j** (175 mg, 0.38 mmol) was taken up in ethyl formate (10 mL, 124 mmol). Sodium methoxide (30 wt.% in MeOH, 0.15 g, 0.83 mmol) was added. After stirring for 2 h at room temperature, the mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **172j** (0.18 g, 98% yield) as a foam. *m/z* = 480 (M+1).

Compound 173j: Compound **172j** (0.18 g, 0.38 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (260 mg, 3.74 mmol) and acetic acid (225 mg, 3.75 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **173j** (0.17 g, 94 % yield) as a foam. *m/z* = 477 (M+1).

Compound 174j: Compound **173j** (170 mg, 0.36 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (250 mg, 1.81 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **174j** (110 mg, 65 % yield) as a foam. *m/z* = 477 (M+1).

T75: Compound **174j** (330 mg, 0.69 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (110 mg, 0.38 mmol) in DMF (1 mL) was added.

After stirring the mixture at 0 °C for 2 h, pyridine (2 mL, 24.8 mmol) was added. The mixture was heated at 60 °C for 4 h, cooled to room temperature, and partitioned between aq. $NaHCO_3$ and EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T75** (165 mg, 50% yield) as a foam. ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.72 (d, J = 5.6 Hz, 1H), 8.30 (qd, J = 1.0, 8.5 Hz, 1H), 7.94 (td, J = 0.9, 8.3 Hz, 1H), 7.81 (dd, J = 0.9, 5.7 Hz, 1H), 7.74 (ddd, J = 1.2, 6.9, 8.2 Hz, 1H), 7.64 (ddd, J = 1.3, 6.9, 8.4 Hz, 1H), 7.47 (m, 2H), 7.28 (m, 1H), 7.19 (ddd, J = 1.0, 8.3, 9.5 Hz, 1H), 2.91 (m, 2H), 2.63 (qd, J = 6.7, 13.3 Hz, 1H), 2.32 (dt, J = 2.7, 12.8 Hz, 1H), 2.16 (m, 1H), 1.87 (m, 1H), 1.58 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 170k: A mixture of compound **88** (1.01g, 2.95 mmol), 7-fluoro-4-quinolinecarboximidamide hydrochloride (1.0 g, 4.43 mmol), and potassium carbonate (1.22 g, 8.85 mmol) in EtOH (25 mL) was heated at reflux for 44 h. The reaction mixture was concentrated and the residue was partitioned between aq. sat. KH_2PO_4 and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude dihydropyrimidine as a yellow glass. The crude product was dissolved in CH_2Cl_2 (15 mL) and the solution was treated with manganese dioxide (88%, 2.27 g, 23.01 mmol). The reaction mixture was stirred under nitrogen at room temperature for 22 h, and filtered through Celite®. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 40% EtOAc in hexanes) to give compound **170k** (1.16 g, 77% yield) as a white glass. *m/z* = 514 (M+1).

Compound 171k: A solution of compound **170k** (1.13 g, 2.20 mmol) in THF (15 mL) was treated with aq. 3 N HCl (7.3 ml, 21.9 mmol) and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo*, and the residue was cooled to 0 °C, neutralized cautiously with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to a give compound **171k** (1.03 g, quantitative yield) as a white glass. m/z = 470 (M+1).

Compound 172k: A solution of compound **171k** (1.03 g, 2.19 mmol) in ethyl formate (15 mL, 186 mmol) was cooled to 0 °C and treated dropwise with sodium methoxide (5.4 M solution in MeOH, 2.04 mL, 11.02 mmol). The cold bath was removed and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo*, and the residue was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give compound **172k** (1.03 g, 94% yield) as an off-white glass. *m/z* = 498 (M+1).

Compound 173k: A solution of compound **172k** (1.03 g, 2.07 mmol) in glacial acetic acid (1.19 mL, 20.7 mmol) and EtOH (10 mL) was treated with hydroxylamine hydrochloride (216 mg, 3.11 mmol). The reaction mixture was stirred under nitrogen at 60 °C for 4 h and at room temperature for 18 h. The solvent was removed *in vacuo*, and the residue was cautiously partitioned between aq. 10% NH_4OH and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **173k** (942 mg, 92% yield) as a pale yellow glass. *m/z* = 495 (M+1).

Compound 174k: A mixture of compound **173k** (942 mg, 1.90 mmol) and potassium carbonate (525 mg, 3.80 mmol) in MeOH (10 mL) was stirred under nitrogen at room temperature for 17 h. The reaction mixture was concentrated, and the residue was partitioned between water and Et_2O. The aqueous phase was cooled in an ice-water bath and acidified with aq. sat. KH_2PO_4. The acidified aqueous mixture was extracted with EtOAc (2 × 50 ml), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **174k** (646 mg, 69% yield) as a white glass. *m/z* = 495 (M+1).

T76: A solution of compound **174k** (646 mg, 1.31 mmol) in degassed DMF (10 mL) was cooled to 0 °C, and treated dropwise with a solution of 1,3-dibromo-5,5-dimethylhydantoin (206 mg, 0.72 mmol) in degassed DMF (3 mL). After stirring at 0 °C for 30 min, anhydrous pyridine (1.06 mL, 13.13 mmol) was added. The cold bath was removed, and the reaction mixture was heated at 60 °C under an argon atmosphere for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T76** (401 mg, 62% yield) as a light yellow glass. ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.5 Hz, 1H), 8.93 (s, 1H), 8.79 (dd, J = 6.1, 9.4 Hz, 1H), 8.02 (d, J = 4.5 Hz, 1H), 7.84 (dd, J = 2.7, 9.9 Hz, 1H), 7.47 (m, 3H), 7.33 (dt, J = 1.0, 7.5 Hz, 1H), 7.24 (m, 1H), 2.90 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.18 (m, 1H), 1.87 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 493 (M+1).

Compound 170l: A mixture of compound **88** (285 mg, 0.83 mmol), 8-fluoro-4-quinolinecarboximidamide hydrochloride (280 mg, 1.24 mmol), and potassium carbonate (343 mg, 2.48 mmol) in EtOH (20 mL) was heated at reflux for 66 h. The reaction mixture was concentrated, and the residue was partitioned between aq. sat. KH_2PO_4 and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude dihydropyrimidine as a yellow glass. The crude product was dissolved in CH_2Cl_2 (15 mL) and the solution was treated with manganese dioxide (88%, 625 mg, 6.33 mmol). The reaction mixture was stirred under nitrogen at room temperature for 23 h and filtered through Celite®. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel, eluting with 40% EtOAc in hexanes) to give compound **170l** (316 mg, 74% yield) as a white glass. *m/z* = 514 (M+1).

Compound 171l: A solution of compound **170l** (316 mg, 0.62 mmol) in THF (15 mL) was treated with aq. 3 N HCl (2.05 mL, 6.15 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo*, and the residue was cooled to 0 °C, neutralized cautiously with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give compound **171l** (276 mg, 95% yield) as a white glass. *m/z* = 470 (M+1).

Compound 172l: A solution of compound **171l** (477 mg, 1.02 mmol) in ethyl formate (15 mL, 186 mmol) was cooled to 0 °C and treated dropwise with sodium methoxide (5.4 M solution in MeOH,

0.94 mL, 5.08 mmol). The cold bath was removed and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo*, and the residue was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **1721** (495 mg, 98% yield) as a yellow glass. *m/z* = 498 (M+1).

Compound 1731: A solution of compound **1721** (490 mg, 0.99 mmol) in glacial acetic acid (0.57 mL, 9.85 mmol) and EtOH (10 mL) was treated with hydroxylamine hydrochloride (103 mg, 1.48 mmol). The reaction mixture was stirred under nitrogen at 60 °C for 4 h and at room temperature for 19 h. The solvent was removed *in vacuo*, and the residue was cautiously partitioned between aq. 10% NH_4OH and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **1731** (567 mg) as an orange glass. *m/z* = 495 (M+1).

Compound 1741: A mixture of compound **1731** (all from the last step) and potassium carbonate (272 mg, 1.97 mmol) in MeOH (10 mL) was stirred under nitrogen at room temperature for 22 h. The reaction mixture was concentrated and the residue was partitioned between water and Et_2O. The aqueous phase was cooled in an ice-water bath and acidified with aq. sat. KH_2PO_4. The acidified aqueous mixture was extracted with EtOAc (2 × 50 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography, eluting with 50% EtOAc in hexanes) to give compound **1741** (300 mg, 62% yield) as a clear glass. *m/z* = 495 (M+1).

T77: A solution of compound **1741** (300 mg, 0.606 mmol) in degassed DMF (10 mL) was cooled to 0 °C, and treated dropwise with a solution of 1,3-dibromo-5,5-dimethylhydantoin (95 mg, 0.332 mmol) in degassed DMF (2 mL). After stirring the mixture at 0 °C for 30 min, anhydrous pyridine (0.49 mL, 6.07 mmol) was added. The cold bath was removed, and the reaction mixture was heated at 60 °C under an argon atmosphere for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T77** (210 mg, 70% yield) as a clear glass. ^1H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 4.4 Hz, 1H), 8.92 (s, 1H), 8.52 (td, J = 1.1, 8.6 Hz, 1H), 8.11 (d, J = 4.4 Hz, 1H), 7.52 (m, 4H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.24 (m, 1H), 2.91 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.8, 12.8 Hz, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 493 (M+1).

Compound 170m: A mixture of compound **88** (1.06 g, 3.08 mmol), 6-methyl-4-pyrimidinecarboximidamide hydrochloride (800 mg, 4.63 mmol), and potassium carbonate (1.28 g, 9.26 mmol) in EtOH (40 mL) was heated at reflux for 96 h, cooled and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine as a yellow glass. The crude product was dissolved in CH_2Cl_2 (20 mL) and the solution was treated with manganese dioxide (88%, 2.38 g, 24.10 mmol). The reaction mixture was stirred under nitrogen at room temperature for 22 h and filtered through Celite®. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel,

eluting with 30% to 100% EtOAc in hexanes) to give compound **170m** (518 mg, 36% yield) as a glass. *m/z* = 461 (M+1).

Compound 171m: A solution of compound **170m** (514 mg, 1.12 mmol) in THF (20 mL) was treated with aq. 3 N HCl (3.73 ml, 11.19 mmol). The reaction mixture was stirred at room temperature for 16 h, and concentrated. The residue was cooled to 0 °C, neutralized cautiously with aq. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 65% to 100% EtOAc in hexanes) to give compound **171m** (264 mg, 57% yield) as a clear glass. *m/z* = 417 (M+1).

Compound 172m: A solution of compound **171m** (264 mg, 0.633 mmol) in ethyl formate (10 mL, 124 mmol) was cooled to 0 °C and treated dropwise with sodium methoxide (5.4 M solution in MeOH, 0.59 ml, 3.19 mmol). The cold bath was removed and the reaction mixture was stirred at room temperature for 14 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated give compound **172m** (274 mg, 97% yield) as an orange glass. *m/z* = 445 (M+1).

Compound 173m: A solution of compound **172m** (270 mg, 0.607 mmol) in glacial acetic acid (0.36 mL, 6.30 mmol) and EtOH (10 mL) was treated with hydroxylamine hydrochloride (66 mg, 0.950 mmol). The reaction mixture was stirred under nitrogen at 60 °C for 4 h and at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was cautiously partitioned between aq. 10% NH_4OH and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **173m** (267 mg, quantitative yield) as an orange-brown glass. *m/z* = 442 (M+1).

Compound 174m: A mixture of compound **173m** (267 mg, 0.605 mmol) and potassium carbonate (167 mg, 1.21 mmol) in MeOH (10 mL) was stirred under nitrogen at room temperature for 16 h. The reaction mixture was concentrated and the residue was partitioned between water and Et_2O. The aqueous phase was cooled in an ice-water bath and acidified with aq. sat. KH_2PO_4. The acidified aqueous mixture was extracted with EtOAc (2 × 50 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **174m** (126 mg, 47% yield) as a yellow glass. *m/z* = 442 (M+1).

T78: A solution of compound **174m** (126 mg, 0.285 mmol) in degassed DMF (5 mL) was cooled to 0 °C, and treated dropwise with a solution of 1,3-dibromo-5,5-dimethylhydantoin (45 mg, 0.156 mmol) in degassed DMF (2 mL). After stirring the mixture at 0 °C for 30 min, anhydrous pyridine (0.23 mL, 2.85 mmol) was added. The cold bath was removed, and the reaction mixture was heated at 60 °C under an argon atmosphere for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **T78** as a yellow glass (83 mg, 66% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 9.34 (d, J = 1.3 Hz, 1H), 9.05 (s, 1H), 8.33 (dd, J = 0.8, 1.2 Hz, 1H), 7.48 (m, 2H), 7.31 (dt, J = 1.0, 7.5

HZ, 1H), 7.19 (ddd, J = 1.0, 8.4, 9.5 Hz, 1H), 2.85 (m, 2H), 2.73 (s, 3H), 2.63 (qd, J = 6.7, 13.4 Hz, 1H), 2.28 (dt, J = 2.7, 12.7 Hz, 1H), 2.13 (m, 1H), 1.82 (m, 1H), 1.57 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 440 (M+1).

Compound 170n: A mixture of compound **88** (701 mg, 2.03 mmol), 4-pyridazinecarboximidamide hydrochloride (484 mg, 3.05 mmol), and potassium carbonate (842 mg, 6.09 mmol) in EtOH (30 mL) was heated at reflux for 67 h. The reaction mixture was concentrated and the residue was partitioned between aq. sat. KH_2PO_4 and EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine as a dark orange glass. The crude product was dissolved in CH_2Cl_2 (20 mL) and the solution was treated with manganese dioxide (88%, 1.56 g, 15.79 mmol). The reaction mixture was stirred under nitrogen at room temperature for 26 h and filtered through Celite®. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **170n** as an oil which crystallized upon standing (276 mg, 30% yield). *m/z* = 447 (M+1).

Compound 171n: A solution of compound **170n** (273 mg, 0.611 mmol) in THF (20 mL) was treated with aq. 3 N HCl (2.04 ml, 6.12 mmol) and the reaction mixture was stirred at room temperature for 17 h, and concentrated. The residue was cooled to 0 °C, neutralized cautiously with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give compound **171n** (256 mg, quantitative yield) as a glass. *m/z* = 403 (M+1).

Compound 172n: A solution of compound **171n** (245 mg, 0.609 mmol) in ethyl formate (8 mL, 99.5 mmol) was cooled to 0 °C and treated dropwise with sodium methoxide (5.4 M solution in MeOH, 0.56 ml, 3.02 mmol). The cold bath was removed and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **172n** (258 mg, 98% yield) as an orange glass. *m/z* = 431 (M+1).

Compound 173n: A solution of compound **172n** (258 mg, 0.599 mmol) in glacial acetic acid (0.35 mL, 5.99 mmol) and EtOH (5 mL) was treated with hydroxylamine hydrochloride (62 mg, 0.892 mmol). The reaction mixture was stirred under nitrogen at 60 °C for 4 h and at room temperature for 21 h. The solvent was removed *in vacuo* and the residue was cautiously partitioned between aq. 10% NH_4OH and CH_2Cl_2. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **173n** (236 mg, 92% yield) as an orange glass. *m/z* = 428 (M+1).

Compound 174n: A mixture of compound **173n** (236 mg, 0.552 mmol) and potassium carbonate (153 mg, 1.10 mmol) in MeOH (10 mL) was stirred under nitrogen at room temperature for 21 h. The reaction mixture was concentrated and the residue was partitioned between water and Et_2O. The aqueous phase was cooled in an ice-water bath and acidified with aq. sat. KH_2PO_4. The acidified aqueous mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 100% EtOAc) to give compound **174n** (164 mg, 69% yield) as a clear glass. *m/z* = 428 (M+1).

T79: A solution of compound **174n** (164 mg, 0.384 mmol) in degassed DMF (5 mL) was cooled to 0 °C, and treated dropwise with a solution of 1,3-dibromo-5,5-dimethylhydantoin (60 mg, 0.210 mmol) in degassed DMF (2 mL). After stirring the mixture at 0 °C for 30 min, anhydrous pyridine (0.31 mL, 3.84 mmol) was added. The cold bath was removed, and the reaction mixture was heated at 60 °C under an argon atmosphere for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 80% EtOAc in hexanes) to give compound **T79** (115 mg, 70% yield) as a yellow oil which crystallized upon standing. ^1H NMR (400 MHz, $CDCl_3$) δ 10.19 (dd, J = 1.3, 2.3 Hz, 1H), 9.40 (dd, J = 1.3, 5.3 Hz, 1H), 8.96 (s, 1H), 8.47 (dd, J = 2.3, 5.3 Hz, 1H), 7.55 (m, 1H), 7.44 (dt, J = 2.0, 7.4 Hz, 1H), 7.35 (dt, J = 1.1, 7.5 Hz, 1H), 7.24 (m, 1H), 2.84 (m, 2H), 2.63 (qd, J = 6.7, 13.4 Hz, 1H), 2.27 (dt, J = 2.8, 12.8 Hz, 1H), 2.15 (m, 1H), 1.81 (ddt, J = 7.2, 10.5, 13.2 Hz, 1H), 1.56 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 426 (M+1).

Compound 175: Compound **88** (172 mg, 0.50 mmol), 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-4-carboximidamide hydrochloride (176 mg, 0.82 mmol) and K_2CO_3 (207 mg, 1.50 mmol) in EtOH (2.5 mL) were heated in a Biotage® microwave synthesizer at 120 °C for 11 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 90% acetone in hexanes) to give the partially purified product (210 mg) as a yellow foamy solid. m/z = 488. The product (210 mg, 0.43 mmol) was dissolved in CH_2Cl_2 (4 mL). DDQ (107 mg, 0.47 mmol) was added. The reaction was stirred at room temperature for 1 h. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **175** (159 g, 66% yield from compound **98**) as a white foamy solid. *m/z* = 486 (M+1).

Compound 176: Compound **175** (157 mg, 0.32 mmol) was taken up in THF (1.1 mL) and MeOH (1.1 mL). Aq. 3 N HCl (1.1 mL, 3.3 mmol) was added. The mixture was stirred overnight at room temperature. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, and concentrated to give compound **176** (146 mg) as a light brown foamy solid. *m/z* = 442 (M+1).

Compound 177: Compound **176** (all from above) was dissolved in ethyl formate (0.8 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.14 mL, 4.94 mmol) was added. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.82 mL, 4.92 mmol), EtOH (3.3 mL) and hydroxylamine hydrochloride (35 mg, 0.50 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 4 h, and concentrated. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50%

acetone in hexanes) to give compound **177** (102 mg, 68% yield from compound **175**) as a white foamy solid. *m/z* = 467 (M+1).

Compound 178: Compound **177** (100 mg, 0.21 mmol) was dissolved in MeOH (2.1 mL). Potassium carbonate (89 mg, 0.64 mmol) was added. The reaction mixture was stirred at room temperature for overnight. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **178** (100 mg, quantitative yield) as a white foamy solid. *m/z* = 467 (M+1).

T80: Compound **178** (100 mg, 0.21 mmol) was dissolved in anhydrous DMF (1 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (31 mg, 0.11 mmol) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (52 μL, 0.64 mmol) was added. The reaction was heated at 55 °C (oil bath) for 2 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **T80** (56 mg, 56% yield) as an off-white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.51 (td, J = 0.9, 5.3 Hz, 1H), 8.00 (td, J = 0.8, 5.3 Hz, 1H), 7.51 (m, 1H), 7.45 (dt, J = 2.0, 7.2 Hz, 1H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.21 (ddd, J = 1.0, 8.3, 9.6 Hz, 1H), 3.47 (t, J = 7.5 Hz, 2H), 3.12 (t, J = 7.8 Hz, 2H), 2.84 (m, 2H), 2.62 (qd, J = 6.7, 13.4 Hz, 1H), 2.22 (m, 4H), 1.80 (m, 1H), 1.55 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 465 (M+1).

Compound 179 and 180: A mixture of compound **12** (1.203 g, 4.00 mmol), 2-fluorophenylboronic acid (559 mg, 4.02 mmol), sodium carbonate (1.28 g, 12.1 mmol), 1,4-dioxane (15 mL) and water (5 mL) in a pressure bottle was sparged with nitrogen for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (294 mg, 0.40 mmol) was added. The nitrogen sparging was continued for another 2 min. The bottle was sealed, and heated at 100 °C for 1 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **179** (675 mg, 47% yield) as a white solid. *m/z* = 359 (M+1). From the column, also get compound **180** (135 mg, 8% yield) as a white foamy solid. *m/z* = 419 (M+1).

Compound 181: Compound **180** (135 mg, 0.32 mmol) was dissolved in ethyl formate (0.78 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.1 mL, 4.76 mmol) was added. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.79 mL, 4.74 mmol), EtOH (3.2 mL) and hydroxylamine hydrochloride (34 mg, 0.49 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 16 h, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **181** (71 mg, 50% yield) as a white foamy solid. *m/z* = 444 (M+1).

Compound 182: Compound **181** (70 mg, 0.16 mmol) was dissolved in MeOH (1.6 mL). Potassium carbonate (65 mg, 0.47 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. EtOAc and aq. 10% NaH_2PO_4 were added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **182** (67 mg, 96% yield) as a white foamy solid. *m/z* = 444 (M+1).

T81: Compound **182** (67 mg, 0.15 mmol) was dissolved in anhydrous DMF (0.75 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (22 mg, 0.077 mmol) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (37 μL, 0.46 mmol) was added. The reaction was heated at 55 °C (oil bath) for 2 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **T81** (18 mg, 27% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.11 (dt, J = 1.9, 7.8, 1H), 7.47 (m, 3H), 7.24 (m, 4H), 2.81 (m, 2H), 2.61 (qd, J = 6.7, 13.4 Hz, 1H), 2.26 (dt, J = 2.7, 12.8 Hz, 1H), 2.11 (m, 1H), 1.80 (m, 1H), 1.54 (s, 3H), 1.32 (d, J = 6.7 Hz, 3H); *m/z* = 442 (M+1).

Compound 184: To a solution of compound **183** (290 mg, 1.41 mmol) in MeCN (7 mL) was added tetrabutylammonium fluoride trihydrate (887 mg, 2.82 mmol) at room temperature. After stirring for 2 h, the reaction mixture was concentrated. The residue was dissolved in 1/1 CH_2Cl_2/toluene, and was purified by flash chromatography (silica gel, eluting with 0% to 10% acetone in hexanes) to give compound **184** (72 mg, 35% yield) as a colorless oil.

Compound 185: A mixture of compound **184** (70 mg, 0.48 mmol), bis(pinacolato)diboron (244 mg, 0.96 mmol), potassium acetate (141 mg, 1.44 mmol), . [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (18 mg, 0.025 mmol) and 1,4-dioxane (1.5 mL) in a vial was sparged with nitrogen for 5 min. The vial was sealed, and heated at 130 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give partially purified compound **185** (103 mg) as a viscous oil, which was used in the next step without further purification. *m/z* = 156 (M-C_6H_9).

Compound 187a: A mixture of 4-chloro-6-fluoro-2-methyl-quinoline (**186a**, 250 mg, 1.28 mmol), bis(pinacolato)diboron (357 mg, 1.41 mmol), potassium acetate (314 mg, 3.20 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (47 mg, 0.064 mmol) and 1,4-dioxane (3 mL) in a vial was sparged with nitrogen for 5 min. The vial was sealed, and heated at 125 °C for 5 h. After the reaction was cooled to room temperature, EtOAc and water were added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with aq. sat. $NaHCO_3$. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash

chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **187a** (140 mg, 38% yield) as a tan solid. *m/z* = 206 (M-C_6H_9).

Compound 187b: A mixture of 4-chloro-6-fluoro-quinoline (**186b**, 463 mg, 2.55 mmol), bis(pinacolato)diboron (712 mg, 2.80 mmol), potassium acetate (626 mg, 6.38 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (98 mg, 0.13 mmol) and 1,4-dioxane (6 mL) in a vial was sparged with N_2 for 5 min. The vial was sealed, and heated at 125 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **187b** (131 mg, 19% yield) as a white solid.

Compound 187c: A mixture of 4-chloro-6,8-difluoro-quinoline (**186c**, 508 mg, 2.55 mmol), bis(pinacolato)diboron (712 mg, 2.80 mmol), potassium acetate (626 mg, 6.38 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (98 mg, 0.13 mmol) and 1,4-dioxane (6 mL) in a vial was sparged with N_2 for 5 min. The vial was sealed, and heated at 125 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **187c** (442 mg, 60% yield) as a white solid.

Compound 188a: A mixture of compound **179** (550 mg, 1.53 mmol), 2-(hydroxymethyl)pyridine-4-boronic acid (351 mg, 2.29 mmol), sodium carbonate (487 mg, 4.59 mmol), 1,4-dioxane (6 mL) and water (2 mL) in a vial was sparged with nitrogen for 5 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (112 mg, 0.15 mmol) was added. The nitrogen sparging was continued for another 2 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 110 °C for 2 h. After the reaction was cooled to room temperature, EtOAc and water were added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with water. The aqueous wash was extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% acetone in hexanes) to give compound **188a** (213 mg, 32% yield) as a light brown foamy solid. *m/z* = 432 (M+1).

Compound 189a: Compound **188a** (211 mg, 0.49 mmol) was dissolved in ethyl formate (1.2 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.7 mL, 7.36 mmol) was added. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (1.23 mL, 7.38 mmol), EtOH (4.8 mL) and hydroxylamine hydrochloride (52 mg, 0.75 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 16 h, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50%

acetone in hexanes) to give compound **189a** (165 mg, 74% yield) as a light yellow foamy solid. *m/z* = 457 (M+1).

Compound 190a: Compound **189a** (62 mg, 0.14 mmol) was dissolved in MeOH (1.4 mL). Sodium methoxide (25 wt.% in methanol, 47 μL, 0.20 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **190a** (56 mg, 90% yield) as a white foamy solid. *m/z* = 457 (M+1).

T82: Compound **190a** (55 mg, 0.12 mmol) was dissolved in benzene (1.2 mL). DDQ (30 mg, 0.13 mmol) was added. The mixture was heated at 85 °C for 30 min, and cooled to rt. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was extracted with CH_2Cl_2. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **T82** (36 mg, 66% yield) as a brown foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.74 (m, 1H), 8.28 (m, 2H), 7.52 (dddd, J = 1.9, 5.3, 7.3, 8.4 Hz, 1H), 7.45 (dt, J = 1.9, 7.4 Hz, 1H), 7.34 (dt, J = 1.1, 7.5 Hz, 1H), 7.22 (ddd, J = 1.0, 8.4, 9.6 Hz, 1H), 4.91 (s, 2H), 3.81 (br s, 1H), 2.83 (m, 2H), 2.63 (m, 1H), 2.26 (dt, J = 2.8, 12.8 Hz, 1H), 2.13 (m, 1H), 1.81 (m, 1H), 1.55 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H); *m/z* = 455 (M+1).

Compound 188b: A mixture of compound **179** (100 mg, 0.28 mmol), compound **185** (partially purified, 100 mg), sodium carbonate (89 mg, 0.84 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (20 mg, 0.027 mmol), 1,4-dioxane (1 mL) and water (0.3 mL) in a vial was sparged with nitrogen for 5 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 120 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **188b** (46 mg, 38% yield) as a viscous oil. *m/z* = 434 (M+1).

Compound 189b: Compound **188b** (46 mg, 0.11 mmol) was dissolved in ethyl formate (0.26 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 0.36 mL, 1.55 mmol) was added. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.26 mL, 1.56 mmol), EtOH (1 mL) and hydroxylamine hydrochloride (12 mg, 0.17 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **189b** (30 mg, 62% yield) as a white foamy solid. *m/z* = 459 (M+1).

Compound 190b: Compound **189b** (28 mg, 0.061 mmol) was dissolved in MeOH (0.6 mL). Sodium methoxide (25 wt.% in methanol, 22 μL, 0.095 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by

flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **190b** (23 mg, 82% yield) as a white foamy solid. *m/z* = 459 (M+1).

T83: Compound **190b** (23 mg, 0.050 mmol) was dissolved in benzene (0.5 mL). DDQ (12 mg, 0.053 mmol) was added. The mixture was heated at 85 °C for 30 min, and cooled to rt. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was stirred until a by-phase solution was obtained, and extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **T83** (19 mg, 83% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.77 (d, J = 5.1 Hz, 1H), 8.48 (s, 1H), 8.32 (m, 1H), 7.53 (dddd, J = 1.9, 5.3, 7.2, 8.3 Hz, 1H), 7.45 (dt, J = 1.9, 7.4 Hz, 1H), 7.34 (dt, J = 1.1, 7.5 Hz, 1H), 7.22 (ddd, J = 1.0, 8.4, 9.6 Hz, 1H), 5.61 (d, J = 46.3 Hz, 2H), 2.83 (m, 2H), 2.63 (qd, J = 6.7, 13.4 Hz, 1H), 2.27 (dt, J = 2.7, 12.8 Hz, 1H), 2.13 (m, 1H), 1.81 (m, 1H), 1.56 (s, 3H), 1.33 (d, J = 6.7 Hz, 3H); *m/z* = 457 (M+1).

Compound 188c: A mixture of compound **179** (150 mg, 0.42 mmol), uinolone-5-boronic acid (108 mg, 0.62 mmol), sodium carbonate (133 mg, 1.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (31 mg, 0.042 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) in a vial was sparged with nitrogen for 5 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 110 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was washed with water. The aqueous wash was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **188c** (192 mg, quantitative yield) as a white solid. *m/z* = 452 (M+1).

Compound 189c: Compound **188c** (192 mg, 0.42 mmol) was dissolved in ethyl formate (1.0 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.5 mL, 6.50 mmol) was added. The mixture was stirred at room temperature for 1 h. THF (0.5 mL) was added. The mixture was stirred for another 1 h, and additional amount of THF (0.5 mL) was added. The mixture was stirred for another 2 h, and cooled to 0 °C. Aq. 6 N HCl (1.08 mL, 6.48 mmol), EtOH (4 mL) and hydroxylamine hydrochloride (45 mg, 0.65 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **189c** (160 mg, 79% yield) as a white foamy solid. *m/z* = 477 (M+1).

Compound 190c: Compound **189c** (157 mg, 0.33 mmol) was dissolved in MeOH (3.3 mL). Sodium methoxide (25 wt.% in methanol, 0.12 mL, 0.52 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **190c** (150 mg, 96% yield) as a white foamy solid. *m/z* = 477 (M+1).

T84: Compound **190c** (150 mg, 0.32 mmol) was dissolved in benzene (3.2 mL). DDQ (75 mg, 0.33 mmol) was added. The mixture was heated at reflux for 1 h, and cooled to rt. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was stirred for 10 min, and extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **T84** (122 mg, 81% yield) as a light yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (ddd, J = 0.9, 1.8, 8.7 Hz, 1H), 8.98 (s, 1H), 8.97 (dd, J = 1.7, 4.4 Hz, 1H), 8.31 (dd, J = 1.3, 7.3 Hz, 1H), 8.27 (td, J = 1.1, 8.5 Hz, 1H), 7.86 (dd, J = 7.3, 8.4 Hz, 1H), 7.49 (m, 3H), 7.32 (dt, J = 1.1, 7.6 Hz, 1H), 7.23 (m, 1H), 2.87 (m, 2H), 2.63 (qd, J = 6.7, 13.5 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.17 (m, 1H), 1.85 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 188d: A mixture of compound **179** (157 mg, 0.437 mmol), compound **187a** (138 mg, 0.481 mmol), sodium carbonate (139 mg, 1.311 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) was sparged with nitrogen for 10 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (36.2 mg, 0.050 mmol) was added and the nitrogen sparging was continued for another 10 min. The reaction vial was sealed and heated to 110 °C in a Biotage® microwave synthesizer for 2 h. The mixture was cooled to room temperature, filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50 % EtOAc in hexanes) to give compound **188d** (220 mg, quantitative yield) as a white foam. *m/z* = 484.2 (M+1).

Compound 189d: Compound **188d** (220 mg, ≤ 0.437 mmol) was dissolved in ethyl formate (1.1 mL, 13.65 mmol) and cooled to 0 °C. Sodium methoxide (25 wt. % in MeOH, 1.6 mL, 6.99 mmol) was added. The mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. Aq. 6 N HCl (1.1 mL, 6.6 mmol), EtOH (4 mL) and hydroxylamine hydrochloride (47.4 mg, 0.682 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, and concentrated. The residue was diluted with aq. sat. $NaHCO_3$, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **189d** (170 mg, 76% yield) as a yellow foam. *m/z* = 509.2 (M+1).

Compound 190d: To a solution of compound **189d** (170 mg, 0.334 mmol) in MeOH (4 mL) was added sodium methoxide (25 wt. % solution in MeOH, 0.115 mL, 0.503 mmol). The reaction mixture was stirred at 55 °C for 2 h, cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4 (4 mL). MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **190d** (130 mg, 76% yield) as an off-white foamy solid. *m/z* = 509.2 (M+1).

T85: A mixture of compound **190d** (130 mg, 0.256 mmol), DDQ (70.0 mg, 0.307 mmol) and benzene (3 mL) was stirred at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60%

acetone in hexanes) to give compound **T85** (50 mg, 39% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.37 (dd, J = 2.9, 10.9 Hz, 1H), 8.11 (dd, J = 5.6, 9.3 Hz, 1H), 7.95 (s, 1H), 7.50 (m, 3H), 7.34 (dt, J = 1.0, 7.5 Hz, 1H), 7.25 (m, 1H), 2.87 (m, 2H), 2.85 (s, 3H), 2.65 (qd, J = 6.6, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.17 (m, 1H), 1.86 (m, 1H), 1.61 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 507.2 (M+1).

Compound 191: A mixture of compound **179** (150 mg, 0.42 mmol), isoquinoline-5-boronic acid (108 mg, 0.62 mmol), sodium carbonate (133 mg, 1.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (31 mg, 0.042 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) in a vial was sparged with nitrogen for 5 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 110 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was washed with water. The aqueous wash was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% acetone in hexanes) to give compound **191** (89 mg, 47% yield) as a brown foamy solid. *m/z* = 452 (M+1).

Compound 192: Compound **191** (87 mg, 0.19 mmol) was dissolved in ethyl formate (0.46 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 0.67 mL, 2.90 mmol) was added. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.48 mL, 2.88 mmol), EtOH (2 mL) and hydroxylamine hydrochloride (20 mg, 0.29 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **192** (75 mg, 82% yield) as a white foamy solid. *m/z* = 477 (M+1).

Compound 193: Compound **192** (73 mg, 0.15 mmol) was dissolved in MeOH (1.5 mL). Potassium carbonate (63 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature for overnight. EtOAc and aq. 10% NaH_2PO_4 were added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% acetone in hexanes) to give compound **193** (66 mg, 90% yield) as a white foamy solid. *m/z* = 477 (M+1).

T86: Compound **193** (65 mg, 0.14 mmol) was dissolved in benzene (1.4 mL). DDQ (33 mg, 0.15 mmol) was added. The mixture was heated at 85 °C for 1 h, and cooled to rt. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was stirred for 10 min, and extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% acetone in hexanes) to give compound **T86** (37 mg, 57% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.99 (s, 1H), 8.67 (td, J = 0.9, 6.0 Hz, 1H), 8.61 (d, J = 6.1 Hz, 1H), 8.51 (td, J = 0.9, 7.3 Hz, 1H), 8.14 (dd, J = 1.1, 8.3 Hz, 1H), 7.78 (dd, J = 7.3, 8.1 Hz, 1H), 7.51 (m, 2H), 7.33 (tt, J = 0.8, 7.6 Hz, 1H), 7.23 (m, 1H), 2.87 (m, 2H), 2.64 (m, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.17 (m, 1H), 1.85 (m, 1H), 1.61 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 475 (M+1).

Compound 194a: A mixture of compound **179** (258 mg, 0.72 mmol), 3,5-dimethylisoxazole-4-boronic acid (152 mg, 1.08 mmol), sodium carbonate (229 mg, 2.16 mmol), 1,4-dioxane (2.7 mL) and water (0.9 mL) in a vial was sparged with nitrogen for 5 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (53 mg, 0.073 mmol) was added. The nitrogen sparging was continued for another 2 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 110 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **194a** (279 mg, 92% yield) as a white foamy solid. *m/z* = 420 (M+1).

Compound 195a: Compound **194a** (277 mg, 0.66 mmol) was dissolved in ethyl formate (1.6 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 2.3 mL, 9.96 mmol) was added. The mixture was stirred at room temperature for 1.5 h, and cooled to 0 °C. Aq. 6 N HCl (1.7 mL, 10.2 mmol), EtOH (6.6 mL) and hydroxylamine hydrochloride (70 mg, 1.01 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 4 h, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **195a** (250 mg, 85% yield) as a white foamy solid. *m/z* = 445 (M+1).

Compound 196a: Compound **195a** (247 mg, 0.56 mmol) was dissolved in MeOH (5.5 mL). Sodium methoxide (25 wt.% in methanol, 0.19 mL, 0.82 mmol) was added. The reaction mixture was stirred at 55 °C for 2 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **196a** (217 mg, 88% yield) as a white foamy solid. *m/z* = 445 (M+1).

T87: Compound **196a** (217 mg, 0.49 mmol) was dissolved in anhydrous DMF (1.2 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (34 mg, 0.12 mmol) in DMF (1.2 mL) was added. The reaction was stirred at 0 °C for 1.5 h. Pyridine (0.12 mL, 1.49 mmol) was added. The reaction was heated at 55 °C (oil bath) for 3 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% acetone in hexanes) to give compound **T87** (177 mg, 82% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.50 (m, 1H), 7.40 (dt, J = 1.9, 7.4 Hz, 1H), 7.30 (dt, J = 1.1, 7.5 Hz, 1H), 7.20 (ddd, J = 1.0, 8.4, 9.7 Hz, 1H), 2.79 (s, 3H), 2.78 (m, 2H), 2.63 (s, 3H), 2.60 (m, 1H), 2.24 (dt, J = 2.8, 12.8 Hz, 1H), 2.10 (m, 1H), 1.76 (dq, J = 7.3, 13.1 Hz, 1H), 1.52 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H); *m/z* = 443 (M+1).

Compound 194b: A mixture of compound **179** (150 mg, 0.42 mmol), 2-methylpyridine-5-boronic acid (86 mg, 0.63 mmol), sodium carbonate (133 mg, 1.25 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) in a vial was sparged with nitrogen for 5 min. [1,1'-

Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (31 mg, 0.042 mmol) was added. The nitrogen sparging was continued for another 2 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 110 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **194b** (132 mg, 76% yield) as a pink foamy solid. *m/z* = 416 (M+1).

Compound 195b: Compound **194b** (130 mg, 0.31 mmol) was dissolved in ethyl formate (0.75 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.1 mL, 4.76 mmol) was added. The mixture was stirred at room temperature for 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.8 mL, 4.8 mmol), EtOH (1.6 mL) and hydroxylamine hydrochloride (33 mg, 0.47 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 6 h, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **195b** (102 mg, 74% yield) as a light yellow foamy solid. *m/z* = 441 (M+1).

Compound 196b: Compound **195b** (100 mg, 0.23 mmol) was dissolved in MeOH (2.2 mL). Sodium methoxide (25 wt.% in methanol, 0.1 mL, 0.43 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to 0 °C. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **196b** (96 mg, 96% yield) as a white foamy solid. *m/z* = 441 (M+1).

T88: Compound **196b** (96 mg, 0.22 mmol) was dissolved in anhydrous DMF (0.55 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (31 mg, 0.11 mmol) in DMF (0.55 mL) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (53 μL, 0.66 mmol) was added. The reaction was heated at 55 °C (oil bath) for 3 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **T88** (71 mg, 74% yield) as an off-white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 2.3 Hz, 1H), 9.01 (s, 1H), 8.62 (dd, J = 2.3, 8.1 Hz, 1H), 7.50 (m, 1H), 7.44 (dt, J = 1.9, 7.4 Hz, 1H), 7.32 (dt, J = 1.0, 7.5 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.20 (ddd, J = 1.0, 8.4, 9.6 Hz, 1H), 2.81 (m, 2H), 2.66 (s, 3H), 2.61 (m, 1H), 2.25 (dt, J = 2.7, 12.7 Hz, 1H), 2.11 (m, 1H), 1.79 (m, 1H), 1.54 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H); *m/z* = 439 (M+1).

Compound 194c: A mixture of compound **179** (150 mg, 0.42 mmol), compound **187b** (125 mg, 0.45 mmol), sodium carbonate (133 mg, 1.25 mmol), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (15 mg, 0.021 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) in a vial was sparged with N_2 for 5 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 110 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was

added. The mixture was washed with water. The aqueous wash was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **194c** (162 mg, 83% yield) as a white foamy solid. *m/z* = 470 (M+1).

Compound 195c: Compound **194c** (160 mg, 0.34 mmol) was dissolved in ethyl formate (0.82 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 0.79 mL, 3.42 mmol) was added. The mixture was stirred at room temperature for 1.5 h, and cooled to 0 °C. Aq. 6 N HCl (0.57 mL, 3.42 mmol), EtOH (3.4 mL) and hydroxylamine hydrochloride (36 mg, 0.52 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **195c** (133 mg, 79% yield) as a white foamy solid. *m/z* = 495 (M+1).

Compound 196c: Compound **195c** (131 mg, 0.27 mmol) was dissolved in MeOH (2.6 mL) and THF (0.5 mL). Sodium methoxide (25 wt.% in methanol, 92 μL, 0.40 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to room temperature. Aq. 10% NaH_2PO_4 were added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **196c** (113 mg, 86% yield) as a white foamy solid. *m/z* = 495 (M+1).

T89: Compound **196c** (112 mg, 0.23 mmol) was dissolved in anhydrous DMF (0.55 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (32 mg, 0.11 mmol) in DMF (0.55 mL) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (55 μL, 0.68 mmol) was added. The reaction was heated at 55 °C (oil bath) for 2.5 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **T89** (73 mg, 65% yield) as an white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 4.5 Hz, 1H), 8.94 (s, 1H), 8.51 (dd, J = 2.9, 11.0 Hz, 1H), 8.22 (dd, J = 5.7, 9.2 Hz, 1H), 8.12 (d, J = 4.6 Hz, 1H), 7.52 (m, 3H), 7.34 (dt, J = 1.1, 7.6 Hz, 1H), 7.24 (m, 1H), 2.90 (m, 2H), 2.65 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 1.61 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 493 (M+1).

Compound 194d: A mixture of compound **179** (150 mg, 0.42 mmol), compound **187c** (182 mg, 0.63 mmol), sodium carbonate (133 mg, 1.25 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (15 mg, 0.021 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) in a vial was sparged with N_2 for 5 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 110 °C for 2 h. After the reaction was cooled to room temperature, EtOAc was added. The mixture was washed with water. The aqueous wash was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give partially purified

compound **194d** (225 mg, quantitative yield) as a white foamy solid, which was used in the next step without further purification. *m/z* = 488 (M+1).

Compound 195d: Compound **194d** (222 mg, 0.46 mmol) was dissolved in ethyl formate (1.1 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.6 mL, 6.93 mmol) was added. The mixture was stirred at room temperature for 1.5 h, and cooled to 0 °C. Aq. 6 N HCl (1.2 mL, 7.2 mmol), EtOH (4.5 mL) and hydroxylamine hydrochloride (48 mg, 0.69 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **195d** (130 mg, 56% yield) as a light yellow foamy solid. *m/z* = 513 (M+1).

Compound 196d: Compound **195d** (128 mg, 0.25 mmol) was dissolved in MeOH (2.5 mL). Sodium methoxide (25 wt.% in methanol, 86 μL, 0.37 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to room temperature. Aq. 10% NaH_2PO_4 were added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **196d** (103 mg, 80% yield) as a white foamy solid. *m/z* = 513 (M+1).

T90: Compound **196d** (103 mg, 0.20 mmol) was dissolved in anhydrous DMF (0.5 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (29 mg, 0.10 mmol) in DMF (0.5 mL) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (49 μL, 0.61 mmol) was added. The reaction was heated at 55 °C (oil bath) for 2.5 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **T90** (74 mg, 72% yield) as an white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 4.5 Hz, 1H), 8.91 (s, 1H), 8.38 (ddd, J = 1.7, 2.7, 10.9 Hz, 1H), 8.21 (d, J = 4.4 Hz, 1H), 7.53 (m, 1H), 7.47 (dt, J = 1.8, 7.4 Hz, 1H), 7.32 (m, 3H), 2.90 (m, 2H), 2.65 (qd, J = 6.7, 13.3 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.18 (m, 1H), 1.85 (m, 1H), 1.61 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 511 (M+1).

Compound 197: To a solution of compound **179** (150 mg, 0.42 mmol) in methylpyrrolidone (0.6 mL) was added 1-methylpiperazine (200 μL, 1.80 mmol). The mixture was heated at 100 °C for 2 h, and cooled to room temperature. EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 10% MeOH in CH_2Cl_2) to give compound **197** (157 mg, 89% yield) as an off-white foamy solid. *m/z* = 423 (M+1).

Compound 198: Compound **197** (210 mg, 0.50 mmol) was dissolved in ethyl formate (1.2 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.7 mL, 7.36 mmol) was added. The mixture was stirred at 0 °C for 1 h, at room temperature for 4 h, and cooled to 0 °C. Aq. 6 N HCl (1.25 mL, 7.50 mmol), EtOH (5 mL) and hydroxylamine hydrochloride (53 mg, 0.76 mmol) were added

sequentially. The mixture was heated at 55 °C (oil bath) for overnight, and concentrated. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to15% MeOH in CH_2Cl_2) to give compound **198** (192 mg, 86% yield) as a yellow foamy solid. *m/z* = 448 (M+1).

Compound 199: Compound **198** (188 mg, 0.42 mmol) was dissolved in MeOH (4 mL). Potassium carbonate (174 mg, 1.26 mmol) was added. The reaction mixture was stirred at room temperature for overnight. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% MeOH in CH_2Cl_2) to give compound **199** (176 mg, 94% yield) as a yellow foamy solid. *m/z* = 448 (M+1).

T91: Compound **199** (175 mg, 0.39 mmol) was dissolved in benzene (4 mL). DDQ (97 mg, 0.43 mmol) was added. The mixture was heated at 85 °C for 1 h, and cooled to rt. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was stirred for 10 min, and extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% acetone in CH_2Cl_2) to give compound **T91** (119 mg, 68% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.41 (dddd, J = 1.9, 5.2, 7.2, 8.2 Hz, 1H), 7.33 (dt, J = 1.9, 7.4 Hz, 1H), 7.24 (dt, J = 1.2, 7.5 Hz, 1H), 7.13 (ddd, J = 1.1, 8.3, 9.6 Hz, 1H), 3.87 (t, J = 5.1 Hz, 4H), 2.52 (m, 7H), 2.36 (s, 3H), 2.13 (dt, J = 2.7, 12.8 Hz, 1H), 1.99 (m, 1H), 1.66 (m, 1H), 1.44 (s, 3H), 1.27 (d, J = 6.7 Hz, 3H); *m/z* = 446 (M+1).

Compound 200: A mixture of compound **88** (900 mg, 2.61 mmol), N-amidinomorpholine hydrobromide (823 mg, 3.92 mmol), and potassium carbonate (1.08 g, 7.81 mmol) in EtOH (50 mL) was heated at reflux for 70 h. The reaction mixture was concentrated and the residue was partitioned between aq. sat. KH_2PO_4 and EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine as a yellow glass. The crude product was dissolved in CH_2Cl_2 (20 mL) and the solution was treated with manganese dioxide (88%, 2.01 g, 20.36 mmol). The reaction mixture was stirred under nitrogen at room temperature for 24 h and filtered through Celite®. The filtrate was concentrated and the residue was purified by flash chromatography (silica gel, eluting with 30% EtOAc in hexanes) to give compound **200** (749 mg, 63% yield) as a clear viscous oil. *m/z* = 454 (M+1).

Compound 201: A solution of compound **200** (745 mg, 1.64 mmol) in THF (30 mL) was treated with aq. 3 N HCl (5.47 mL, 16.4 mmol) and the reaction mixture was stirred at room temperature for 17 h. The solvent was removed *in vacuo* and the residue was cooled to 0 °C, neutralized cautiously with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give compound **201** (565 mg, 84% yield) as an oil. *m/z* = 410 (M+1).

Compound 202: A solution of compound **201** (564 mg, 1.38 mmol) in ethyl formate (18 ml, 224 mmol) was cooled to 0 °C and treated dropwise with sodium methoxide (5.4 M solution in MeOH, 1.28 ml, 6.91 mmol). The cold bath was removed and the reaction mixture was stirred at room temperature for

18 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **202** (604 mg, quantitative yield) as an orange oil. *m/z* = 438 (M+1).

Compound 203: A solution of compound **202** (604 mg, 1.38 mmol) in glacial acetic acid (0.80 mL, 13.8 mmol) and EtOH (12 mL) was treated with hydroxylamine hydrochloride (144 mg, 2.07 mmol). The reaction mixture was stirred under nitrogen at 60 °C for 4 h and at room temperature for 22 h. The solvent was removed *in vacuo* and the residue was cautiously partitioned between aq. 10% NH_4OH and EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **203** (541 mg, 90% yield) as a light brown glass. *m/z* = 435 (M+1).

Compound 204: A mixture of compound **203** (541 mg, 1.25 mmol) and potassium carbonate (346 mg, 2.50 mmol) in MeOH (20 mL) was stirred under nitrogen at room temperature for 21 h. The reaction mixture was concentrated and the residue was partitioned between water and Et_2O. The aqueous phase was cooled in an ice-water bath and acidified with aq. sat. KH_2PO_4. The acidified aqueous mixture was extracted with EtOAc (2 × 40 ml) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 40% EtOAc in hexanes) to give compound **204** (383 mg, 71% yield) as a clear glass. *m/z* = 435 (M+1).

T92: A solution of compound **204** (327 mg, 0.752 mmol) in anhydrous DMF (5 mL) was cooled to 0 °C, and was treated dropwise with a solution of 1,3-dibromo-5,5-dimethylhydantoin (118 mg, 0.413 mmol) in anhydrous DMF (2 mL). After stirring the mixture at 0 °C for 30 min, anhydrous pyridine (0.61 ml, 7.56 mmol) was added. The cold bath was removed, and the reaction mixture was heated at 60 °C under an argon atmosphere for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 30% EtOAc in hexanes) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 0% to 3% EtOAc in CH_2Cl_2) to give compound **T92** (160 mg, 49% yield) as a glass. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.42 (ddd, J = 1.9, 5.2, 7.2, 8.4 Hz, 1H), 7.32 (dt, J = 1.9, 7.4 Hz, 1H), 7.24 (m, 1H), 7.14 (ddd, J = 1.0, 8.4, 9.6 Hz, 1H), 3.82 (m, 8H), 2.55 (m, 3H), 2.14 (dt, J = 2.8, 12.8 Hz, 1H), 2.00 (m, 1H), 1.67 (dq, J = 7.4, 13.2 Hz, 1H), 1.44 (s, 3H), 1.27 (d, J = 6.8 Hz, 3H); *m/z* = 433 (M+1).

Compound 205: A mixture of compound **95** (245 mg, 0.63 mmol), cyclopropylboronic acid (90 mg, 1.05 mmol), potassium phosphate (660 mg, 3.11 mmol), tricyclohexylphosphine (54 mg, 0.19 mmol), palladium acetate (24 mg, 0.11 mmol), toluene (4 mL) and water (0.2 mL) in a vial was sparged with N_2 for 3 min. The vial was sealed, and heated in a Biotage® microwave synthesizer at 130 °C for 4 h. After the reaction was cooled to room temperature, the mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give the compound **205** (123 mg, 49% yield) as a white solid. *m/z* = 398 (M+1).

Compound 206: Compound **205** (121 mg, 0.30 mmol) was dissolved in ethyl formate (0.73 mL) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.05 mL, 4.55 mmol) was added. The mixture was stirred at room temperature for 6 h, and cooled to 0 °C. Aq. 6 N HCl (0.76 mL, 4.56 mmol), EtOH (3 mL) and hydroxylamine hydrochloride (43 mg, 0.62 mmol) were added sequentially. The mixture was heated overnight at 55 °C (oil bath), and concentrated. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extract dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **206** (72 mg, 56% yield) as a white foamy solid. *m/z* = 423 (M+1).

Compound 207: Compound **206** (72 mg, 0.17 mmol) was dissolved in MeOH (1.7 mL). Sodium methoxide (25 wt.% in methanol, 60 μL, 0.26 mmol) was added. The reaction mixture was stirred at 55 °C for 1 h, and cooled to room temperature. Aq. 10% NaH_2PO_4 were added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **207** (54 mg, 75% yield) as a white foamy solid. *m/z* = 423 (M+1).

T93: Compound **207** (54 mg, 0.13 mmol) was dissolved in anhydrous DMF (0.6 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (18 mg, 0.063 mmol) was added. The reaction was stirred at 0 °C for 1 h. Pyridine (31 μL, 0.38 mmol) was added. The reaction was heated at 55 °C (oil bath) for 5 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **T93** (35 mg, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 4.4 Hz, 1H), 8.91 (s, 1H), 8.67 (dd, J = 1.2, 8.8 Hz, 1H), 8.20 (dd, J = 0.8, 8.4 Hz, 1H), 7.94 (d, J = 4.5 Hz, 1H), 7.76 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H), 7.61 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 3.22 (ddd, J = 1.2, 6.8, 17.9 Hz, 1H), 3.03 (ddd, J = 7.7, 11.2, 18.3 Hz, 1H), 2.63 (qd, J = 6.7, 13.4 Hz, 1H), 2.30 (m, 1H), 2.22 (dt, J = 2.7, 12.8 Hz, 1H), 2.15 (m, 1H), 1.91 (ddt, J = 6.8, 11.4, 13.3 Hz, 1H), 1.54 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H), 1.35 (m, 2H), 1.17 (m, 2H); m/z = 421.2 (M+1).

Compound 94: Compound **93** (1 g, 2.40 mmol) was taken up in toluene (10 mL). Phosphorus(V) oxychloride (4 g, 26.09 mmol) was added. The mixture was heated in Biotage® Initiator™ microwave synthesizer at 100 °C for 60 min, cooled, and poured into ice. After sitting for 10 min, the mixture was extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated. The crude product was mixed in benzene (100 mL), and treated with ethylene glycol (1 g, 16.11 mmol) and *p*-toluenesulfonic acid monohydrate (60 mg, 0.32 mmol). The mixture was refluxed for 16 h with a Dean-Stark trap, cooled to room temperature, and washed with water. The organic extract was dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **94** (550 mg, 53% yield) as a light color solid. *m/z* = 436 (M+1).

Compound 208: A mixture of compound **94** (550 mg, 1.26 mmol) was taken up in THF (10 mL). Cyclobutanol (200 mg, 2.77 mmol) and NaH (60% dispersion in mineral oil, 120 mg, 3.00 mmol) were added. The reaction was stirred at 60 °C for 16 h, cooled, and concentrated. The residue was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **208** (500 mg, 84 % yield) as a white solid. *m/z* = 472 (M+1).

Compound 209: A mixture of compound **208** (500 mg, 1.06 mmol) was taken up in THF (10 mL), and aq. 3 N HCl (5 mL, 15.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, filtered, and concentrated to give compound **209** (450 mg, 99% yield) as a white solid. *m/z* = 428 (M+1).

Compound 210: Compound **209** (450 mg, 1.05 mmol) was taken up in ethyl formate (15 mL, 186 mmol). Sodium methoxide (30 wt.% in MeOH, 200 mg, 1.11 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **210** (430 mg, 90% yield) as a foam. *m/z* = 456 (M+1).

Compound 211: Compound **210** (430 mg, 0.94 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (660 mg, 9.50 mmol) and acetic acid (550 mg, 9.15 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **211** (425 mg, 99% yield) as a foam. *m/z* = 453 (M+1).

Compound 212: Compound **211** (425 mg, 0.94 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (650 mg, 4.70 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **212** (235 mg, 55% yield) as a foam. *m/z* = 453 (M+1).

T94: Compound **212** (235 mg, 0.52 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (82 mg, 0.29 mmol) in DMF (1 mL) was added. The reaction stirred at 0 °C for 2 h, and pyridine (2 mL, 24.8 mmol) was added. The reaction was heated at 60 °C for 4 h, cooled, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T94** (115 mg, 49% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 4.4 Hz, 1H), 8.88 (s, 1H), 8.76 (m, 1H), 8.21 (m, 1H), 7.95 (d, J = 4.5 Hz, 1H), 7.77 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H), 7.62 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 5.34 (m, 1H), 2.96 (ddd, J = 1.1, 6.8, 18.8 Hz, 1H), 2.72 (ddd, J = 7.6, 11.3, 18.9 Hz, 1H), 2.61 (td, J = 6.7, 12.8 Hz, 1H), 2.56 (m, 2H), 2.22 (m, 4H), 1.80 (m, 3H), 1.51 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H); *m/z* = 451 (M+1).

Compound 213: To a suspension of sodium hydride (60% dispersion in mineral oil, 37 mg, 0.93 mmol) in THF (1 mL) was added cyclobutanemethanol (86 μL, 0.91 mmol) at room temperature. A solution of compound **94** (200 mg, 0.46 mmol) in THF (3.5 mL) was added at room temperature. The mixture was stirred at room temperature for 30 min, at 50 °C for 2 h, and cooled to room temperature. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **213** (203 mg, 91% yield).

Compound 214: To a stirring solution of compound **213** (203 mg, 0.42 mmol) in MeOH (1.5 mL) and THF (1.5 mL) was added aq. 3 N HCl (1.4 mL, 4.2 mmol) at room temperature. The reaction was stirred at room temperature for 2 h, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, and concentrated to give compound **214** (193 mg, quantitative yield) as a white solid, which was used in the next step without further purification. *m/z* = 442 (M+1).

Compound 215: Compound **214** (193 mg, ≤ 0.42 mmol) in ethyl formate (1.9 mL, 23.62 mmol) was cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 2.7 mL, 11.69 mmol) was added. The mixture was stirred at room temperature for 30 min. THF (0.5 mL) was added. After stirring for another 1.5 h, additional amount of THF (0.5 mL) was added. The reaction was stirred for another 1 h, and cooled to 0 °C. Aq. 6 N HCl (2.0 mL, 12 mmol), EtOH (8 mL) and hydroxylamine hydrochloride (84 mg, 1.21 mmol) were added sequentially. The mixture was heated overnight at 55 °C (oil bath), and concentrated. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extract dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **215** (145 mg, 71% yield) as a white foamy solid. *m/z* = 467 (M+1).

Compound 216: Compound **215** (143 mg, 0.31 mmol) was dissolved in MeOH (3 mL). Potassium carbonate (123 mg, 0.89 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **216** (122 mg, 85% yield) as a white foamy solid. *m/z* = 467 (M+1).

T95: Compound **216** (121 mg, 0.26 mmol) was dissolved in anhydrous DMF (1.3 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (37 mg, 0.13 mmol) was added. The reaction was stirred at 0 °C for 1 h, and at room temperature for 1 h. Pyridine (63 μL, 0.78 mmol) was added. The reaction was heated at 55 °C (oil bath) for 3 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **T95** (87 mg, 72% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 4.5 Hz, 1H), 8.88 (s, 1H), 8.77 (ddd, J = 0.6, 1.5, 8.6 Hz, 1H), 8.22 (td, J = 1.0, 8.4 Hz, 1H), 7.98 (d, J = 4.5 Hz,

1H), 7.78 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H), 7.63 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 4.49 (m, 1H), 4.45 (dd, J = 6.5, 10.8 Hz, 1H), 2.96 (ddd, J = 1.0, 6.6, 18.7 Hz, 1H), 2.78 (m, 2H), 2.61 (qd, J = 6.7, 13.4 Hz, 1H), 2.17 (m, 4H), 1.92 (m, 5H), 1.52 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 465 (M+1).

Compound 217a: To a suspension of sodium hydride (60% dispersion in mineral oil, 37 mg, 0.93 mmol) in THF (1 mL) was added cyclohexanol (0.097 mL, 0.92 mmol) at room temperature. The mixture was stirred for 10 min, and added at 0 °C to a solution of compound **94** (200 mg, 0.46 mmol) in THF (3.6 mL). The mixture was stirred at room temperature for 30 min, at 50 °C for 2 h, and cooled to room temperature. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **217a** (208 mg, 90% yield) as a white foam.

Compound 218a: To a stirring solution of **217a** (208 mg, 0.416 mmol) in MeOH (1.5 mL) and THF (1.5 mL) was added aq. 3 N HCl (1.5 mL, 4.5 mmol) at room temperature. The reaction was stirred at room temperature for 2 h, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated to give compound **218a** (200 mg, quantitative yield) as a white foam. *m/z* = 456.2 (M+1).

Compound 219a: Compound **218a** (200 mg, ≤ 0.416 mmol) was dissolved in ethyl formate (1.06 mL, 13.16 mmol) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.5 mL, 6.56 mmol) was added. The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. Aq. 6 N HCl (1.09 mL, 6.54 mmol), EtOH (2 mL) and hydroxylamine hydrochloride (46 mg, 0.66 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, cooled to room temperature, and concentrated. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **219a** (88 mg, 44% yield) as a pale yellow foam.

Compound 220a: To a solution of Compound **219a** (88 mg, 0.18 mmol) in MeOH (1 mL) was added sodium methoxide (25 wt. % solution in MeOH, 0.063 mL, 0.27 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 2 h, cooled to 0 °C, and neutralized with aq. 10% NaH_2PO_4 (3 mL). MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4 filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **220a** (42 mg, 48 % yield) as an off-white foamy solid. *m/z* = 481.2 (M+1).

T96: Compound **220a** (42 mg, 0.087 mmol) was dissolved in anhydrous DMF (0.5 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (12.5 mg, 0.043 mmol) in DMF (0.5 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, and pyridine (0.021 mL, 0.262 mmol) was added. The reaction mixture was heated at 55 °C for 3 h, and then cooled to room temperature. CH_2Cl_2 was added, and the mixture was washed with water. The organic layer was dried with Na_2SO_4,

filtered and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **T96** (20 mg, 48% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 4.5 Hz, 1H), 8.89 (s, 1H), 8.81 (m, 1H), 8.21 (m, 1H), 7.99 (d, J = 4.4 Hz, 1H), 7.77 (ddd, J = 1.4, 6.7, 8.4 Hz, 1H), 7.62 (ddd, J = 1.3, 6.8, 8.3 Hz, 1H), 5.32 (tt, J = 3.8, 8.4 Hz, 1H), 2.94 (dd, J = 6.7, 18.6 Hz, 1H), 2.72 (ddd, J = 7.5, 11.2, 18.8 Hz, 1H), 2.61 (qd, J = 6.7, 13.3 Hz, 1H), 2.19 (m, 2H), 2.02 (m, 2H), 1.83 (m, 3H), 1.55 (m, 6H), 1.52 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 479.2 (M+1).

Compound 217b: To a suspension of sodium hydride (60% dispersion in mineral oil, 37 mg, 0.93 mmol) in THF (1 mL) was added cyclopentanol (0.084 mL, 0.92 mmol) at room temperature. The mixture was stirred for 10 min, and added at 0 °C to a solution of compound **94** (200 mg, 0.46 mmol) in THF (3.6 mL). The mixture was stirred at room temperature for 30 min, at 50 °C for 2 h, and cooled to room temperature. Aq. sat. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **217b** (160 mg, 72% yield) as a white foam.

Compound 218b: To a stirring solution of **217b** (160 mg, 0.329 mmol) in MeOH (1.0 mL) and THF (1.0 mL) was added aq. 3 N HCl (1.1 mL, 3.3 mmol) at room temperature. The reaction was stirred at room temperature for 2 h, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated to give compound **218b** (150 mg, quantitative yield) as a white foam. *m/z* = 442.2 (M+1).

Compound 219b: Compound **218b** (150 mg, ≤ 0.329 mmol) was dissolved in ethyl formate (0.82 mL, 10.2 mmol) and cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 1.2 mL, 5.24 mmol) was added. The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. Aq. 6 N HCl (0.85 mL, 5.10 mmol), EtOH (2 mL) and hydroxylamine hydrochloride (35.4 mg, 0.51 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, cooled to room temperature, and concentrated. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **219b** (100 mg, 65% yield) as a white foam. *m/z* = 467.2 (M+1).

Compound 220b: To a solution of Compound **219b** (100 mg, 0.214 mmol) in MeOH (2 mL) was added sodium methoxide (25 wt. % in MeOH, 0.074 mL, 0.323 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 2 h, cooled to 0 °C, and neutralized with aq. 10% NaH_2PO_4 (4 mL). MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4 filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **220b** (88 mg, 88% yield) as an off-white foamy solid. *m/z* = 467.2 (M+1).

T97: Compound **220b** (87 mg, 0.186 mmol) was dissolved in anhydrous DMF (1.0 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (26.6 mg, 0.093 mmol) in DMF (0.5

mL) was added. The reaction was stirred at 0 °C for 1 h, and pyridine (0.045 mL, 0.56 mmol) was added. The reaction mixture was heated at 55 °C for 3 h, and then cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene (10 mL). The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **T97** (55 mg, 64% yield) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 4.4 Hz, 1H), 8.89 (s, 1H), 8.81 (ddd, J = 0.6, 1.4, 8.6 Hz, 1H), 8.21 (ddd, J = 0.7, 1.4, 8.5 Hz, 1H), 7.98 (d, J = 4.5 Hz, 1H), 7.77 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H), 7.62 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 5.63 (tt, J = 2.7, 6.1 Hz, 1H), 2.90 (dd, J = 6.4, 18.8 Hz, 1H), 2.66 (m, 2H), 1.97 (m, 11H), 1.52 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 465.2 (M+1).

Compound 221a and 221b: A mixture of compound **94** (600 mg, 1.37 mmol) was taken up in DMF (5 mL). Methanesulfonamide (660 mg, 6.94 mmol) and NaH (60% dispersion in mineral oil, 170 mg, 4.25 mmol) were added. The reaction was stirred at 80 °C for 16 h, cooled and concentrated. The residue was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **221a** (250 mg, 37% yield) and **221b** (225 mg, 37% yield) as foamy solid. *m/z* = 495 (compound **221a**, M+1). *m/z* = 445 (compound **221b**, M+1).

Compound 222a: Compound **221a** (250 mg, 0.51 mmol) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, filtered and concentrated to give compound **222a** (180 mg, 79% yield) as a foam. *m/z* = 451 (M+1).

Compound 223a: Compound **222a** (180 mg, 0.40 mmol) was taken up in ethyl formate (10 mL, 124 mmol). Sodium methoxide (30 wt.% in MeOH, 150 mg, 0.83 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **223a** (175 mg, 92% yield) as a foam. *m/z* = 479 (M+1).

Compound 224a: Compound **223a** (175 mg, 0.37 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (255 mg, 3.67 mmol) and acetic acid (220 mg, 3.66 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **224a** (130 mg, 75% yield) as a foam. *m/z* = 476 (M+1).

Compound 225a: Compound **224a** (130 mg, 0.27 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (230 mg, 1.66 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was

purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **225a** (110 mg, 85% yield) as a foam. *m/z* = 476 (M+1).

T98: Compound **225a** (110 mg, 0.23 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (37 mg, 0.13 mmol) in DMF (1 mL) was added. The reaction stirred at 0 °C for 2 h, and pyridine (2 mL, 24.8 mmol) was added. The reaction was heated at 60 °C for 4 h, cooled, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T98** (45 mg, 41% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 4.4 Hz, 1H), 8.85 (m, 2H), 8.23 (d, J = 8.5 Hz, 1H), 8.00 (m, 1H), 7.80 (dd, J = 6.8, 8.6 Hz, 1H), 7.68 (dd, J = 6.9, 8.5 Hz, 1H), 3.44 (br s, 3H), 2.83 (dd, J = 6.7, 17.7 Hz, 1H), 2.65 (m, 2H), 2.28 (dd, J = 7.6, 14.1 Hz, 1H), 2.19 (t, J = 12.9 Hz, 1H), 1.88 (m, 1H), 1.54 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H); *m/z* = 474 (M+1).

Compound 222b: Compound **221b** (225 mg, 0.51 mmol) was taken up in THF (6 mL), and aq. 3 N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. saturated $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, filtered and concentrated to give compound **222b** (205 mg, quantitative yield) as a foam. *m/z* = 401 (M+1).

Compound 223b: Compound **222b** (205 mg, 0.51 mmol) was taken up in ethyl formate (10 mL, 124 mmol). Sodium methoxide (30 wt.% in MeOH, 210 mg, 1.17 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **223b** (220 mg, quantitative yield) as a foam. *m/z* = 429 (M+1).

Compound 224b: Compound **223b** (220 mg, 0.51 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (360 mg, 5.18 mmol) and acetic acid (310 mg, 5.16 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered, and concentrated to give compound **224b** (200 mg, 92 % yield) as a foam. *m/z* = 426 (M+1).

Compound 225b: Compound **224b** (200 mg, 0.47 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (390 mg, 2.82 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **225b** (140 mg, 70% yield) as a foam. *m/z* = 426 (M+1).

T99: Compound **225b** (140 mg, 0.33 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin (52 mg, 0.18 mmol) in DMF (1 mL) was added. The reaction stirred at 0 °C for 2 h, and pyridine (2 mL, 24.8 mmol) was added. The reaction was heated at 60 °C for 4 h, cooled, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T99** (45 mg, 32% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 4.5 Hz, 1H), 8.87 (s, 1H), 8.82 (m, 1H), 8.20 (m, 1H), 7.99 (d, J =

4.5 Hz, 1H), 7.75 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.60 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 3.16 (s, 6H), 2.91 (m, 2H), 2.61 (qd, J = 6.7, 13.3 Hz, 1H), 2.22 (m, 2H), 1.77 (m, 1H), 1.51 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 424 (M+1).

Compound 226a: A mixture of compound **94** (300 mg, 0.69 mmol), 3,5-dimethylisoxazole-4-boronic acid (145.4 mg, 1.03 mmol), sodium carbonate (219 mg, 2.06 mmol), 1,4-dioxane (2.7 mL) and water (0.9 mL) was sparged with nitrogen for 10 min. [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50 mg, 0.069 mmol) was added and nitrogen sparging was continued for another 10 min. The reaction vial was sealed and heated to 110 °C in a Biotage® microwave synthesizer for 2 h. The mixture was cooled to room temperature, filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 0% to 50 % EtOAc in hexanes) to give compound **226a** (290 mg, 85% yield) as a white foam. *m/z* = 497.2 (M+1).

Compound 227a: To a mixture of compound **226a** (290 mg, 0.584 mmol) in MeOH (1.9 mL) and THF (1.9 mL) was added aq. 3 N HCl (1.9 mL, 5.7 mmol) at room temperature. After stirring for 2 h, the mixture was concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated to give compound **227a** (240 mg, 91% yield) as a white solid. *m/z* = 453.2 (M+1).

Compound 228a: Compound **227a** (240 mg, 0.530 mmol) was dissolved in ethyl formate (1.3 mL, 16.2 mmol) and cooled to 0 °C. Sodium methoxide (25 wt.% in MeOH, 1.8 mL, 7.87 mmol) was added The mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. Aq. 6 N HCl (1.3 mL, 7.8 mmol), EtOH (2 mL) and hydroxylamine hydrochloride (55 mg, 0.79 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, and concentrated. The residue was diluted with aq. sat. $NaHCO_3$, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **228a** (220 mg, 87% yield) as a white foam. *m/z* = 478.2 (M+1).

Compound 229a: To a solution of Compound **228a** (220 mg, 0.46 mmol) in MeOH (4 mL) was added sodium methoxide (25 wt. % solution in MeOH, 0.16 mL, 0.70 mmol). The reaction mixture was stirred at 55 °C for 1.5 h, cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4. MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extract was dried with Na_2SO_4 and filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **229a** (160 mg, 73% yield) as an off-white solid. *m/z* = 478.2 (M+1).

T100: Compound **229a** (160 mg, 0.335 mmol) was dissolved in anhydrous DMF (2 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (47.9 mg, 0.168 mmol) in DMF (1.3 mL) was added. The reaction was stirred at 0 °C for 1 h, and pyridine (0.081 mL, 1.0 mmol) was added. The mixture was heated at 55 °C for 3 h, and then cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, filtered and concentrated.

The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 70% acetone in hexanes) to give compound **T100** (20 mg, 13% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, J = 4.5 Hz, 1H), 8.91 (s, 1H), 8.71 (m, 1H), 8.26 (m, 1H), 8.03 (d, J = 4.5 Hz, 1H), 7.80 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 7.65 (ddd, J = 1.3, 6.8, 8.3 Hz, 1H), 2.82 (m, 2H), 2.66 (qd, J = 6.6, 13.3 Hz, 1H), 2.42 (s, 3H), 2.29 (s, 3H), 2.27 (m, 2H), 1.89 (m, 1H), 1.48 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H); *m/z* = 476.2 (M+1).

Compound 226b: A mixture of compound **94** (300 mg, 0.69 mmol), 4-(benzyl(methyl)carbamoyl)phenylboronic acid (278 mg, 1.03 mmol), sodium carbonate (219 mg, 2.06 mmol), 1,4-dioxane (3.3 mL) and water (1.1 mL) was sparged with nitrogen for 10 min. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (50 mg, 0.069 mmol) was added and nitrogen sparging was continued for another 10 min. The reaction vial was sealed and heated to 110 °C in a Biotage® microwave synthesizer for 2 h. The mixture was cooled to room temperature, filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 0% to 60 % EtOAc in hexanes) to give compound **226b** (416 mg, 97% yield) as a light yellow foam. *m/z* = 625.3 (M+1).

Compound 227b: To a solution of compound **226b** (416 mg, 0.665 mmol) in MeOH (2.2 mL) and THF (2.2 mL) was added aq. 3 N HCl (2.2 mL, 6.6 mmol) at room temperature. After stirring for 2 h, the mixture was concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4 , filtered and concentrated to give compound **227b** (359 mg, 93% yield) as a yellow foam. *m/z* = 581.3 (M+1).

Compound 228b: Compound **227b** (355 mg, 0.611 mmol) was dissolved in ethyl formate (1.5 mL, 18.6 mmol) and cooled to 0 °C. Sodium methoxide (25 wt. % in MeOH, 2.1 mL, 9.17 mmol) was added. The mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. Aq. 6 N HCl (1.53 mL, 9.2 mmol), EtOH (9 mL), and hydroxylamine hydrochloride (63.7 mg, 0.92 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, and concentrated. The residue was diluted with aq. sat. $NaHCO_3$, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **228b** (183 mg, 49 % yield) as a white foam. *m/z* = 606.3 (M+1).

Compound 229b: To a solution of compound **228b** (183 mg, 0.302 mmol) in MeOH (4 mL) was added sodium methoxide (25 wt. % solution in MeOH, 0.105 mL, 0.458 mmol). The reaction mixture was stirred at 55 °C for 1.5 h, cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4. MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **229b** (140 mg, 76% yield) as an off-white solid. *m/z* = 606.2 (M+1).

T101: Compound **229b** (140 mg, 0.231 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (33 mg, 0.115 mmol) in DMF (1 mL)

was added. The reaction mixture was stirred at 0 °C for 1 h, and pyridine (0.056 mL, 0.693 mmol) was added. The mixture was heated at 55 °C for 3 h, and then cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene (10 mL). The residue was purified by flash chromatography (silica gel, eluted with 0% to 20% acetone in hexanes) to give compound **T101** (110 mg, 79% yield) as a light yellow solid. **T101** is a 1:1 mixture of amide isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (m, 1H), 8.93 (m, 1H), 8.68 (m, 1H), 8.22 (d, J = 8.6 Hz, 1H), 8.00 (m, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.63 (m, 5H), 7.36 (m, 4H), 7.18 (d, J = 7.0 Hz, 1H), [4.79 (s), 4.56 (s), 1:1, 2H], [3.07 (s), 2.91 (s), 1:1, 3H], 3.02 (m, 2H), 2.64 (m, 1H), 2.24 (m, 2H), 1.84 (m, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 604.2 (M+1).

Compound 230a: A mixture of compound **94** (250 mg, 0.573 mmol), 2-furanboronic acid (96.3 mg, 0.86 mmol), sodium carbonate (182 mg, 1.72 mmol), 1,4-dioxane (3 mL) and water (1 mL) was sparged with nitrogen for 10 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (42 mg, 0.057 mmol) was added and nitrogen sparging was continued for another 10 min. The reaction vial was sealed and heated to 110 °C in a Biotage® microwave synthesizer for 2 h. The mixture was cooled to room temperature, filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with, 0% to 60 % EtOAc in hexanes) to give compound **230a** (226 mg, 84% yield) as a white foam. *m/z* = 468.2 (M+1).

Compound 231a: To a solution of compound **230a** (226 mg, 0.483 mmol) in MeOH (1.6 mL) and THF (1.6 mL) was added aq. 3 N HCl (1.6 mL, 4.8 mmol) at room temperature. The mixture was stirred 2 h at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated to give compound **231a** (190 mg, 93% yield) as a yellow foam. *m/z* = 424.2 (M+1).

Compound 232a: Compound **231a** (190 mg, 0.449 mmol) was dissolved in ethyl formate (1.1 mL, 13.7 mmol) and cooled to 0 °C. Sodium methoxide (25 wt. % in MeOH, 1.5 mL, 6.56 mmol) was added. The mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. Aq. 6 N HCl (1.1 mL, 6.6 mmol), EtOH (6 mL) and hydroxylamine hydrochloride (46.8 mg, 0.67 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, and concentrated. The residue was diluted with aq. sat. $NaHCO_3$, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 20% acetone in hexanes) to give compound **232a** (171 mg, 85% yield) as a white foam. *m/z* = 449.2 (M+1).

Compound 233a: To a solution of Compound **232a** (171 mg, 0.381 mmol) in MeOH (4 mL) was added sodium methoxide (25 wt. % solution in MeOH, 0.13 mL, 0.57 mmol). The reaction mixture was stirred at 55 °C for 1.5 h, cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4. MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue

was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **233a** (110 mg, 64% yield) as an off-white foam. *m/z* = 449.2 (M+1).

T102: A mixture of compound **233a** (90 mg, 0.201 mmol), DDQ (55 mg, 0.241 mmol) and benzene (2 mL) was stirred at reflux for 3 h. The reaction mixture was cooled to room temperature and then concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **T102** (67 mg, 75% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 4.5 Hz, 1H), 8.94 (s, 1H), 8.78 (m, 1H), 8.23 (m, 1H), 8.05 (d, J = 4.5 Hz, 1H), 7.79 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 7.73 (td, J = 0.7, 1.6 Hz, 1H), 7.64 (ddd, J = 1.3, 6.8, 8.3 Hz, 1H), 7.45 (td, J = 0.8, 3.6 Hz, 1H), 6.65 (ddd, J = 0.6, 1.8, 3.6 Hz, 1H), 3.49 (dd, J = 6.5, 18.9 Hz, 1H), 3.28 (ddd, J = 7.4, 11.2 18.8 Hz, 1H), 2.64 (qd, J = 6.7, 13.5 Hz, 1H), 2.28 (m, 2H), 1.92 (dq, J = 6.4, 13.1 Hz, 1H), 1.58 (s, 3H), 1.37 (d, J = 6.7 Hz, 3H); *m/z* = 447.1 (M+1).

Compound 230b: A mixture of compound **94** (216 mg, 0.496 mmol), 2-benzofuranboronic acid (120.4 mg, 0.74 mmol), sodium carbonate (158 mg, 1.49 mmol)), 1,4-dioxane (3 mL) and water (1 mL) was sparged with nitrogen for 10 min. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (36.2 mg, 0.049 mmol) was added and nitrogen sparging was continued for another 10 min. The reaction vial was sealed and heated to 110 °C in a Biotage® microwave synthesizer for 2 h. The mixture was cooled to room temperature, filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50 % EtOAc in hexanes) to give compound **230b** (230 mg, 90% yield) as a white foam. *m/z* = 518.2 (M+1).

Compound 231b: To a solution of compound **230b** (230 mg, 0.444 mmol) in MeOH (2 mL) and THF (2 mL) was added aq. 3 N HCl (2 mL, 6 mmol). The mixture was stirred for 2 h at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated to give compound **231b** (195 mg, 93% yield) as a yellow foam. *m/z* = 474.2 (M+1).

Compound 232b: Compound **231b** (195 mg, 0.412 mmol) was dissolved in ethyl formate (0.99 mL, 12.32 mmol) and cooled to 0 °C. Sodium methoxide (25 wt. % in MeOH, 1.4 mL, 6.12 mmol) was added. The mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. Aq. 6 N HCl (1.1 mL, 6.6 mmol), EtOH (6 mL) and hydroxylamine hydrochloride (42.9 mg, 0.617 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, and concentrated. The residue was diluted with aq. sat. $NaHCO_3$, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **232b** (136 mg, 66% yield) as a white foam. *m/z* = 499.2 (M+1).

Compound 233b: To a solution of Compound **232b** (130 mg, 0.261 mmol) in MeOH (4 mL) was added sodium methoxide (25 wt. % solution in MeOH, 0.089 mL, 0.39 mmol). The reaction mixture was stirred at 55 °C for 1.5 h, cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4. MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue

was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **233b** (93 mg, 71% yield) as an off-white foam. *m/z* = 499.2 (M+1).

T103: A mixture of compound **233b** (93 mg, 0.186 mmol), DDQ (50.8 mg, 0.224 mmol) and benzene (2 mL) was stirred at reflux for 3 h. The reaction mixture was cooled to room temperature then concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% acetone in hexanes) to give compound **T103** (38 mg, 41% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, J = 4.5 Hz, 1H), 8.95 (s, 1H), 8.82 (m, 1H), 8.26 (m, 1H), 8.09 (d, J = 4.4 Hz, 1H), 7.81 (m, 2H), 7.73 (d, J = 7.6 Hz, 1H), 7.68 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.45 (ddd, J = 1.3, 7.1, 8.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 3.68 (dd, J = 6.5, 18.9 Hz, 1H), 3.46 (ddd, J = 7.7, 11.2, 18.9 Hz, 1H), 2.67 (qd, J = 6.7, 13.3 Hz, 1H), 2.32 (m, 2H), 1.98 (m, 1H), 1.61 (s, 3H), 1.40 (d, J = 6.7 Hz, 3H); *m/z* = 497.2 (M+1).

Compound 234: A mixture of compound **94** (250 mg, 0.57 mmol), 5-methyl-2-furanboronic acid pinacol ester (0.17 mL, 0.86 mmol) and sodium carbonate (182 mg, 1.72 mmol) was sparged with nitrogen for 6 min. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (42 mg, 0.057 mmol) was added and mixture was held under nitrogen stream for 1 min. The reaction vial was sealed and heated to 110 °C in Biotage® microwave synthesizer for 2 h. The mixture was cooled to room temperature, filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 0% to 60 % EtOAc in hexanes) to give compound **234** (345 mg) as a white foam. *m/z* = 482.2 (M+1).

Compound 235: To a mixture of compound **234** (345 mg, ≤ 0.57 mmol) in MeOH (2.2 mL) and THF (2.2 mL) was added aq. 3 N HCl (2.2 mL, 6.6 mmol) at room temperature. After stirring for 3 h, the mixture was concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with brine, dried with $NaSO_4$, filtered and concentrated to give compound **235** (207 mg, 82% yield from compound **94**). *m/z* = 438.2 (M+1).

Compound 236: Compound **235** (206 mg, 0.47 mmol) was dissolved in ethyl formate (1.6 mL, 19.8 mmol) and cooled to 0 °C. Sodium methoxide (25 wt.% in MeOH, 1.6 mL, 7.05 mmol) was added. The mixture was stirred at room temperature for 2 h. Aq. 6 N HCl (1.2 mL, 7.2 mmol), EtOH (3 mL) and hydroxylamine hydrochloride (49 mg, 0.71 mmol) were added sequentially. The mixture was heated to 55 °C for 3 h, and concentrated. The residue was diluted with aq. sat. $NaHCO_3$ and the mixture was extracted twice with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 65% acetone in hexanes) to give compound **236** (107 mg, 49% yield). *m/z* = 463.2 (M+1).

Compound 237: To a solution of compound **236** (107 mg, 0.23 mmol) in MeOH (3.3 mL) was added sodium methoxide (25 wt. % solution in MeOH, 0.08 mL, 0.35 mmol). The reaction mixture was stirred at 55 °C for 2 h, cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 65% acetone in hexanes) to give compound **237** (76 mg, 71% yield) as an off-white solid. *m/z* = 463.2 (M+1).

T104: Compound **237** (76 mg, 0.17 mmol) was dissolved in anhydrous DMF (1.8 mL), and the solution was cooled to 0 °C. 1,3-dibromo-5,5-dimethylhydantoin (24.5 mg, 0.086 mmol) in DMF (0.7 mL) was added. The reaction was stirred at 0 °C for 1.5 h, and pyridine (0.041 mL, 0.51 mmol) was added. The mixture was heated at 55 °C for 2.5 h and then cooled to room temperature. EtOAc (100 mL) was added. The mixture was washed with aq. sat. NaHCO3 (10 mL), aq. 10% Na2SO3 (10 mL) and brine (10 mL). The organic extract was dried with Na_2SO_4, filtered and concentrated. The residual pyridine was removed by azeotropic evaporation with toluene. The residue was purified by flash chromatography (silica gel, eluting with 0% to 65% acetone in hexanes) to give compound **T104** (42 mg, 56% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (d, J = 4.5 Hz, 1H), 8.94 (s, 1H), 8.81 (dd, J = 1.4, 8.6 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 4.4 Hz, 1H), 7.77 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H), 7.63 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.36 (d, J = 3.4 Hz, 1H), 6.26 (m, 1H), 3.45 (dd, J = 6.2, 19.0 Hz, 1H), 3.22 (ddd, J = 7.7, 11.2, 18.7 Hz, 1H), 2.62 (m, 1H), 2.47 (s, 3H), 2.29 (m, 2H), 1.92 (m, 1H), 1.56 (s, 3H), 1.37 (d, J = 6.7 Hz, 3H); *m/z* = 461.2 (M+1).

Compound 238: A mixture of compound **94** (510 mg, 1.17 mmol), zinc cyanide (206 mg, 1.85 mmol) and tetrakis(triphenylphosphine)palladium(0) (135 mg, 0.12 mmol) were weighed in a vial. The vial was sealed, and kept under vacuum. *N,N*-Dimethylacetamide (sparged with N_2 for 5 min, 5 mL) was added. The vial was filled with argon, heated at 120 °C for 3 h, and cooled to room temperature. EtOAc was added. The mixture was filtered through a plug of Celite®, and eluted with EtOAc. The filtrate was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **238** (433 mg, 87% yield) as a white foamy solid. *m/z* = 427 (M+1).

Compound 239: To a suspension of compound **238** (100 mg, 0.23 mmol) in water (1.25 mL) was added aq. H_2SO_4 (prepared by diluting *conc.* H_2SO_4 (1.25 mL, 22.5 mmol) with water (0.63 mL) at room temperature. The mixture was heated overnight at 100 °C, cooled to room temperature, and poured into ice (30 g). The mixture was adjusted to pH ~ 8 using aq. 1 N NaOH, and extracted with EtOAc. The aqueous phase was treated with NaH_2PO_4 to adjust pH ~ 5, and extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated to give compound **239** (90 mg, 96% yield) as a brown solid. *m/z* = 402 (M+1).

Compound 240: Compound **239** (88 mg, 0.22 mmol) in ethyl formate (0.53 mL) was cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 0.76 mL, 3.29 mmol) was added. The mixture was stirred at room temperature for 30 min. THF (0.5 mL) was added. The reaction was stirred for another 1 h, and cooled to 0 °C. Aq. 6 N HCl (0.55 mL, 3.30 mmol), EtOH (2.2 mL) and hydroxylamine hydrochloride (23 mg, 0.33 mmol) were added sequentially. The mixture was heated overnight at 55 °C (oil bath), and concentrated. CH_2Cl_2 and water were added. The mixture was extracted repeatedly with EtOAc. The combined organic extract dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (C18, eluting with 0% to 50% MeCN in water) to give compound **240** (51 mg, 55% yield) as a yellow foamy solid. *m/z* = 427 (M+1).

Compound 241: To a mixture of compound **240** (50 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was added oxalyl chloride (24 μL, 0.30 mmol) and DMF (1 drop) sequentially at 0 °C. The reaction was stirred at room temperature for 4 h, and concentrated. The crude acid chloride was dissolved in in CH_2Cl_2 (1.2 mL), and cooled to 0 °C. Triethylamine (65 μL, 0.47 mmol) and acetamide oxime (13 mg, 0.18 mmol) were added sequentially. After the reaction was stirred at room temperature for 1 h, EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 65% acetone in hexanes) to give compound **241** (25 mg, 44% yield) as a yellow foamy solid. *m/z* = 483 (M+1).

Compound 242: Compound **241** (25 mg, 0.052 mmol) in toluene (5 mL) was heated at reflux with Dean-Stark apparatus for 4 h, and cooled to room temperature. The mixture was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **242** (21 mg, 44% yield) as a white foamy solid. *m/z* = 465 (M+1).

Compound 243: Compound **242** (20 mg, 0.043 mmol) was dissolved in MeOH (0.5 mL). Potassium carbonate (18 mg, 0.13 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **243** (15 mg, 75% yield) as a white foamy solid. *m/z* = 465 (M+1).

T105: Compound **243** (15 mg, 0.032 mmol) was dissolved in benzene (1 mL). DDQ (8 mg, 0.035 mmol) was added. The mixture was heated at 85 °C for 1 h, and cooled to room temperature. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was stirred at room temperature for 10 min, and extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **T105** (11 mg, 73% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, J = 4.5 Hz, 1H), 8.90 (s, 1H), 8.82 (m, 1H), 8.25 (m, 1H), 8.12 (d, J = 4.4 Hz, 1H), 7.81 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.69 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 3.67 (dd, J = 6.1, 19.7 Hz, 1H), 3.38 (ddd, J = 7.8, 11.1, 19.5 Hz, 1H), 2.65 (m, 1H), 2.58 (s, 3H), 2.31 (m, 2H), 1.95 (m, 1H), 1.61 (s, 3H), 1.38 (d, J = 6.8 Hz, 3H); *m/z* = 463 (M+1).

Compound 244: A mixture of hydroxylamine hydrochloride (66 mg, 0.94 mmol) and $NaHCO_3$ (79 mg, 0.94 mmol) in EtOH (1 mL) was heated at reflux for 1 h, and cooled to 0 °C. Compound **238** (200 mg, 0.47 mmol) and EtOH (0.5 mL) were added, and the mixture was stirred at room temperature for 5 h. EtOAc and water were added. The mixture was extracted with EtOAc. The combined organic extract was dried with Na_2SO_4 and concentrated to give compound **244** (198 mg, 92% yield) as a white solid. *m/z* = 460 (M+1).

Compound 246: To a mixture of compound **244** (196 mg, 0.43 mmol) in AcOH (1 mL) was added acetic anhydride (60 μL, 0.64 mmol) at room temperature. The mixture was stirred at room temperature for 20 min, heated at 100 °C for 16 h, and cooled to room temperature. Toluene was added,

and the mixture was concentrated to dryness to give a mixture of compound **245** and **246**. The mixture was dissolved in MeOH (2.8 mL). Aq. 3 N HCl (1.4 mL, 4.2 mmol) was added. The reaction was stirred at room temperature for 4 h. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **246** (159 mg, 85% yield) as a light yellow foamy solid. *m/z* = 440 (M+1).

Compound 247: Compound **246** (155 mg, 0.35 mmol) in ethyl formate (0.85 mL) was cooled to 0 °C. Sodium methoxide (25 wt.% in methanol, 0.81 mL, 3.51 mmol) was added. The mixture was stirred at room temperature for 2 h, and cooled to 0 °C. Aq. 6 N HCl (0.58 mL, 3.48 mmol), EtOH (3.5 mL) and hydroxylamine hydrochloride (37 mg, 0.53 mmol) were added sequentially. The mixture was heated at 55 °C (oil bath) for 6 h, and concentrated. Aq. sat. $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic extract dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **247** (67 mg, 41% yield) as a yellow foamy solid. *m/z* = 465 (M+1).

Compound 248: Compound **247** (67 mg, 0.14 mmol) was dissolved in MeOH (1.4 mL). Potassium carbonate (60 mg, 0.43 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. Aq. 10% NaH_2PO_4 was added. The mixture was extracted with EtOAc. The organic extract was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **248** (53 mg, 79% yield) as a yellow foamy solid. *m/z* = 465 (M+1).

T106: Compound **248** (53 mg, 0.11 mmol) was dissolved in benzene (1.1 mL). DDQ (29 mg, 0.12 mmol) was added. The mixture was heated at 85 °C for 1 h, and cooled to room temperature. CH_2Cl_2 and aq. sat. $NaHCO_3$ were added. The mixture was stirred at room temperature for 5 min, and extracted with CH_2Cl_2. The combined organic extract was washed with aq. sat. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give partially purified product, which was purified again by flash chromatography (silica gel, eluting with 0% to 10% MeOH in CH_2Cl_2) compound **T106** (28 mg, 53% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 4.6 Hz, 1H), 8.91 (s, 1H), 8.69 (dd, J = 1.3, 8.6 Hz, 1H), 8.23 (m, 1H), 8.04 (d, J = 4.5 Hz, 1H), 7.79 (ddd, J = 1.4, 6.8, 8.5 Hz, 1H), 7.66 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 3.51 (m, 1H), 3.29 (ddd, J = 7.6, 11.1, 19.2 Hz, 1H), 2.75 (s, 3H), 2.65 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (m, 2H), 1.92 (m, 1H), 1.60 (s, 3H), 1.37 (d, J = 6.7 Hz, 3H); *m/z* = 463 (M+1).

Compound 249: A mixture of compound **94** (250 mg, 0.573 mmol) in 1,4-dioxane (3 mL) was sparged with N_2 for 10 min. 2-(Tri-n-butylstannyl)thiazole (0.144 mL, 0.459 mmol) and tetrakis(triphenylphosphine)palladium(0) (26.5 mg, 0.023 mmol) were added sequentially, and nitrogen sparging was continued for another 10 min. The reaction mixture was refluxed for 8 h, cooled to room temperature, and concentrated. The residue diluted with EtOAc, and treated with aq. 10% KF (10 mL). The mixture was stirred at room temperature for 30 minutes, and filtered. The filtrate was washed with

water. The organic extract was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60 % acetone in hexanes) to give compound **249** (168 mg, 60% yield) as a white foam. *m/z* = 485.2 (M+1).

Compound 250: To a solution of compound **249** (168 mg, 0.346 mmol) in MeOH (2 mL) and THF (2 mL) was added aq. 3 N HCl (2 mL, 6 mmol) at room temperature. The reaction mixture was stirred for 2 h, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60 % acetone in hexanes) to give compound **250** (112 mg, 73% yield) as a yellow solid. *m/z* = 441.1 (M+1).

Compound 251: Compound **250** (112 mg, 0.254 mmol) was dissolved in ethyl formate (0.613 mL, 7.62 mmol) and cooled to 0 °C. Sodium methoxide (25 wt. % in MeOH, 0.872 ml, 3.81 mmol) was added. The mixture was stirred at room temperature for 2 h, and then cooled to 0 °C. Aq. 6 N HCl (0.64 mL, 3.84 mmol), EtOH (4 mL) and hydroxylamine hydrochloride (27 mg, 0.389 mmol) were added sequentially. The mixture was heated at 55 °C for 16 h, and concentrated. The residue was diluted with aq. sat. $NaHCO_3$, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 50% acetone in hexanes) to give compound **251** (50 mg, 42% yield) as a yellow foam. *m/z* = 466.1 (M+1).

Compound 252: To a solution of Compound **251** (50 mg, 0.107 mmol) in MeOH (1 mL) was added potassium carbonate (22.2 mg, 0.161 mmol). The reaction mixture was stirred at room temperature for 4 h, cooled to 0 °C, and neutralized by adding aq. 10% NaH_2PO_4. MeOH was removed by evaporation. The residue was diluted with water, and the mixture was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 40% acetone in hexanes) to give compound **252** (20 mg, 40% yield) as an off-white foam. *m/z* = 466.1 (M+1).

T107: A mixture of compound **252** (20 mg, 0.043 mmol), DDQ (11.7 mg, 0.051 mmol) and benzene (1 mL) was stirred at reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **T107** (5.4 mg, 27% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 4.4 Hz, 1H), 9.02 (s, 1H), 8.93 (s, 1H), 8.80 (dd, J = 1.3, 8.8 Hz, 1H), 8.55 (s, 1H), 8.25 (m, 1H), 8.08 (d, J = 4.4 Hz, 1H), 7.81 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.67 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 3.33 (ddd, J = 1.4, 6.9, 17.8 Hz, 1H), 3.20 (ddd, J = 7.5, 10.9, 18.0 Hz, 1H), 2.67 (qd, J = 6.7, 13.4 Hz, 1H), 2.41 (m, 1H), 2.33 (dt, J = 2.7, 12.7 Hz, 1H), 2.01 (m, 1H), 1.60 (s, 3H), 1.39 (d, J = 6.7 Hz, 3H); *m/z* = 464.1 (M+1).

Compound 253: In a sealable vial, a mixture of compound **9** (assume 16.78 mmol), 2-methyl-4-quinolinecarboximidamide hydrochloride (3.90 g, 17.59 mmol) and potassium carbonate (4.86 g, 35.16 mmol) in EtOH (17 mL) was flushed with nitrogen. The vial was sealed and heated at 40 °C for 2 days. The mixture was concentrated, and the residue was diluted with EtOAc (150 mL) and water (50 mL), and

heated at 65 °C until all solid was in solution (~1.5 h). The layers were separated, and the organic extract was washed with aq. sat. KH_2PO_4 (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, concentrated. The residue was purified by flash chromatography (silica gel, eluting with 5% MeOH in $CHCl_3$) to give compound **253** (5.35 g, 74% yield) as an orange foamy solid. *m/z* = 432 (M+1).

Compound 254: In a microwave vessel, a mixture of compound **253** (1.78 g, 4.12 mmol) and phosphorus(V) oxychloride (3.8 mL, 40.7 mmol) in toluene (12 mL) was flushed with nitrogen. The vial was sealed and heated in Biotage® microwave synthesizer at 100 °C for 1 h. The mixture was cooled to room temperature, and carefully poured into a stirring suspension of $NaHCO_3$ (17 g, 205 mmol) in water (100 mL). After stirring for 30 min, the mixture was extracted with EtOAc (200 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give a mixture of ketal and ketone (1.70 g) as dark yellow foamy solid. The crude product was dissolved in benzene (50 mL), and treated with ethylene glycol (2.3 mL, 41.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.078 g, 0.41 mmol). The mixture was refluxed with Dean-Stark trap for 4 h, cooled, and partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **254** (1.56 g, 84% yield) as an off-white foamy solid. *m/z* = 450 (M+1).

Compound 255a: In a sealable vial, a mixture of compound **254** (0.40 g, 0.89 mmol), 3-fluorophenylboronic acid (0.19 g, 1.36 mmol), potassium phosphate (0.57 g, 2.68 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.10 g, 0.088 mmol) in 1,4-dioxane (9 mL) was degassed with nitrogen. The vial was sealed and heated at 90 °C for 16 h. After cooling to room temperature, the mixture partitioned between aq. 1N NaOH (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **255a** (0.40 g, 88% yield) as a light yellow foamy solid. *m/z* = 510 (M+1).

Compound 256a: A solution of compound **255a** (0.40 g, 0.79 mmol) and aq. 3 N HCl (5 mL, 15 mmol) in MeOH (10 mL) was stirred at room temperature overnight, and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **256a** (0.32 g, 88% yield) as a light yellow foamy solid. *m/z* = 466 (M+1).

Compound 257a: To a stirring solution at room temperature of compound **256a** (0.32 g, 0.68 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.37 mL, 2.05 mmol). The mixture was stirred for 2 h, and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **257a** (0.29 g, 85% yield) as yellow orange foamy solid. *m/z* = 494 (M+1).

Compound 258a: To a solution of compound **257a** (0.29 g, 0.59 mmol) in EtOH (10 mL) was added acetic acid (0.34 mL, 5.93 mmol) and hydroxylamine hydrochloride (0.062 g, 0.89 mmol). The

mixture was stirred at 60 °C under nitrogen for 2 h, at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **258a** (0.27 g, 94% yield) as a yellow-orange foamy solid. *m/z* = 491 (M+1).

Compound 259a: A solution of compound **258a** (0.27 g, 0.55 mmol) in MeOH (6 mL) was treated with potassium carbonate (0.38 g, 2.75 mmol). The mixture was stirred at room temperature under nitrogen for 16 h, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **259a** (0.18 g, 67% yield) as a light yellow foamy solid. *m/z* = 491(M+1).

T108: To a stirring solution at 0 °C under nitrogen of compound **259a** (0.18 g, 0.37 mmol) in degassed DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.057 g, 0.20 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (0.30 mL, 3.72 mmol) was added. The ice-bath was removed, and the mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T108** (0.069 g, 39% yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.58 (dd, J = 0.8, 8.4, 1H), 8.13 (dd, J = 0.4, 8.4 Hz, 1H), 7.87 (s, 1H), 7.74 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.57 (ddd, J = 1.3, 6.8, 8.3 Hz, 1H), 7.51 (dt, J = 5.6, 8.0 Hz, 1H), 7.40 (td, J = 1.2, 7.7 Hz, 1H), 7.34 (ddd, J = 1.6, 2.6, 9.3 Hz, 1H), 7.22 (ddt, J = 1.0, 2.6, 8.3 Hz, 1H), 3.03 (m, 2H), 2.86 (s, 3H), 2.65 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.21 (tdd, J = 2.8, 5.8, 12.2 Hz, 1H), 1.84 (ddt, J = 7.4, 10.1 13.5 Hz, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 489 (M+1).

Compound 255b:. In a sealable vial, a mixture of compound **254** (0.40 g, 0.89 mmol), 4-fluorophenylboronic acid (0.19 g, 1.36 mmol), potassium phosphate (0.57 g, 2.69 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.10 g, 0.088 mmol) in 1,4-dioxane (9 mL) was degassed with nitrogen. The vial was sealed and heated at 90 °C for 16 h. The mixture was cooled and partitioned between aq. 1 N NaOH (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **255b** (0.39 g, 86% yield) as a light yellow foamy solid. *m/z* = 510 (M+1).

Compound 256b: A solution of compound **255b** (0.39 g, 0.77 mmol) and aq. 3 N HCl (2.6 mL, 7.8 mmol) in MeOH (8 mL) was stirred at room temperature overnight, and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give compound **256b** (0.35 g, 98% yield) as a light yellow foamy solid. *m/z* = 466 (M+1).

Compound 257b: To a stirring solution at room temperature of compound **256b** (0.35 g, 0.75 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH,

0.41 g, 2.28 mmol). The mixture was stirred for 2 h and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **257b** (0.31 g, 83% yield) as an orange foamy solid. *m/z* = 494 (M+1).

Compound 258b: A solution of compound **257b** (310 mg, 0.627 mmol) in glacial acetic acid (0.36 ml, 6.28 mmol) and EtOH (10 mL) was treated with hydroxylamine hydrochloride (65 mg, 0.935 mmol). The reaction mixture was stirred under nitrogen at 60 °C for 4 h and at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was cautiously partitioned between aq. 10% NH_4OH and EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **258b** (357 mg) as a yellow glass. *m/z* = 491 (M+1).

Compound 259b: A mixture of compound **258b** (all from the last step) and potassium carbonate (201 mg, 1.45 mmol) in MeOH (10 mL) was stirred under nitrogen at room temperature for 16 h. The reaction mixture was concentrated and the residue was partitioned between water and Et_2O. The aqueous phase was cooled in an ice-water bath and acidified with aq. sat. KH_2PO_4. The acidified aqueous mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **259b** (167 mg, 54% yield from compound **257b**) as a white glass. *m/z* = 491 (M+1).

T109: A solution of compound **259b** (167 mg, 0.34 mmol) in degassed DMF (5 mL), was cooled to 0 °C, and was treated dropwise with a solution of 1,3-dibromo-5,5-dimethylhydantoin (53 mg, 0.185 mmol) in degassed DMF (2 mL). After stirring the mixture at 0 °C for 30 min, anhydrous pyridine (0.27 mL, 3.35 mmol) was added. The cold bath was removed, and the reaction mixture was heated at 60 °C under an argon atmosphere for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T109** (90 mg, 54% yield) as a white amorphous solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.58 (dd, J = 1.4, 8.6 Hz, 1H), 8.13 (ddd, J = 0.6, 1.3, 8.5 Hz, 1H), 7.86 (s, 1H), 7.74 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.65 (m, 2H), 7.56 (ddd, J = 1.3, 6.9, 8.4 Hz, 1H), 7.22 (m, 2H), 3.03 (m, 2H), 2.86 (s, 3H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.20 (tdd, J = 2.8, 5.9, 13.7 Hz, 1H), 1.84 (ddt, J = 7.2, 10.2, 13.5 Hz, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 489 (M+1).

Compound 260a: Sodium hydride (60% dispersion in mineral oil, 0.066 g, 1.65 mmol) was added portionwise to a stirring solution of cyclobutanol (0.12 g, 1.66 mmol) in THF (10 mL) at room temperature over 10 min. The mixture was stirred for 1 h, and was treated with compound **254** (0.50 g, 1.11 mmol). The mixture was heated at 60 °C under nitrogen overnight, cooled to room temperature, and quenched with aq. sat. KH_2PO_4 (50 mL). The solvent was evaporated *in vacuo* and the residue was extracted with EtOAc (50 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with

50% EtOAc in hexanes) to give compound **260a** (0.54 g, quantitative yield) as an off-white foamy solid. *m/z* = 486 (M+1).

Compound 261a: A solution of compound **260a** (0.54 g, assume 1.11 mmol) and aq. 3 N HCl (3.7 mL, 11.1 mmol) in MeOH (11 mL) was stirred at room temperature overnight. The mixture was concentrated, cooled, basified with aq. 10% NH_4OH and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **261a** (0.52g) as an off-white foamy solid. *m/z* = 442 (M+1).

Compound 262a: To a stirring solution at room temperature of compound **261a** (all from the last step) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.61 mL, 3.39 mmol). The mixture was stirred for 2 h and partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **262a** (0.51 g, 98% yield from compound **260a**) as an orange foamy solid. *m/z* = 470 (M+1).

Compound 263a: To a solution of compound **262a** (0.51 g, 1.08 mmol) in EtOH (10 mL) was added acetic acid (0.62 mL, 10.83 mmol) and hydroxylamine hydrochloride (0.12 g, 1.73 mmol). The mixture was stirred at 60 °C under N_2 for 2 h, at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **263a** (0.47 g, 93% yield) as a yellow-orange foamy solid. *m/z* = 467 (M+1).

Compound 264a: A solution of compound **263a** (0.47 g, 1.01 mmol) in MeOH (10 mL) was treated with potassium carbonate (0.71 g, 5.14 mmol). The sample was stirred at room temperature under nitrogen for 16 h, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **264a** (0.33 g, 70% yield) as a light yellow foamy solid. *m/z* = 467 (M+1).

T110: To a stirring solution at 0 °C under nitrogen of compound **264a** (0.33 g, 0.71 mmol) in degassed DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.11 g, 0.38 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (0.57 mL, 7.06 mmol) was added. The ice-bath was removed, and the mixture was heated at 60 °C for 4 h, cooled and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T110** (0.11 g, 33% yield) as a light yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.61 (dd, J = 0.8, 8.8 Hz, 1H), 8.12 (dd, J = 0.8, 8.4 Hz, 1H), 7.79 (s, 1H), 7.73 (ddd, J = 1.5, 6.8, 8.4 Hz, 1H), 7.54 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 5.34 (m, 1H), 2.95 (ddd, J = 0.8, 6.8, 18.8 Hz, 1H), 2.86 (s, 3H), 2.72 (ddd, J = 7.6, 11.5, 18.8 Hz, 1H), 2.60 (qd, J = 6.9, 13.8 Hz, 1H), 2.52 (m, 2H), 2.22 (m, 4H), 1.80 (m, 3H), 1.51 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 465 (M+1).

Compound 260b: Compound **254** (800 mg, 1.78 mmol) was taken up in THF (10 mL). Cyclopentanol (600 mg, 6.97 mmol) and sodium hydride (60% dispersion in mineral oil, 280 mg, 7.00 mmol) were added. The mixture was stirred at 60 °C for 16 h, cooled, and concentrated. The residue was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **260b** (850 mg, 95 % yield) as a foam. *m/z* = 500 (M+1).

Compound 261b: A mixture of compound **260b** (850 mg, 1.70 mmol) was taken up in THF (10 mL), and aq. 3 N HCl (5 mL, 15 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, then dried over $MgSO_4$, filtered and concentrated to give compound **261b** (775 mg, quantitative yield) as a foam. *m/z* = 456 (M+1).

Compound 262b: Compound **261b** (775 mg, 1.70 mmol) was taken up in ethyl formate (15 mL, 186.5 mmol). Sodium methoxide (30 wt.% in methanol, 600 mg, 3.33 mmol) was added. After stirring at room temperature for 2 h, the mixture was neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried over $MgSO_4$, filtered and concentrated to give compound **262b** (825 mg, quantitative yield) as a foam. *m/z* = 484 (M+1).

Compound 263b: Compound **262b** (825 mg, 1.70 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (1.2 g, 17.26 mmol) and AcOH (1 g, 16.65 mmol) were added. The mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc, and washed with aq. $NaHCO_3$. The organic extract was dried over $MgSO_4$, filtered and concentrated to give compound **263b** (820 mg, quantitative yield) as a foam. *m/z* = 481 (M+1).

Compound 264b: Compound **263b** (820 mg, 1.70 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (1.2 g, 8.68 mmol) was added. The mixture was stirred at room temperature overnight, neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **264b** (570 mg, 70% yield) as a foam. *m/z* = 481 (M+1).

T111: Compound **264b** (570 mg, 1.19 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (210 mg, 1.31 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred at 0 °C for 2 h, and pyridine (2 mL, 24.8 mmol) was added. The ice-bath was removed. The reaction mixture heated at 60 °C for 4 h, cooled and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T111** (75 mg, 13% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.66 (dd, J = 1.3, 8.7 Hz, 1H), 8.12 (m, 1H), 7.82 (s, 1H), 7.72 (ddd, J = 1.4, 6.8, 8.3 Hz, 1H), 7.54 (ddd, J = 1.3, 6.7, 8.3 Hz, 1H), 5.62 (tt, J = 2.7, 6.1 Hz, 1H), 2.90 (m, 1H), 2.86 (s, 3H), 2.65 (m, 2H), 2.18 (m, 2H), 1.81 (m, 9H), 1.51 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 479 (M+1).

Compound 265: Compound **9** (1.1 g, 3.71 mmol) was taken up in EtOH (15 mL). Quinazoline-4-carboximidamide hydrochloride (0.6 g, 2.88 mmol) and potassium carbonate (1 g, 7.24) were added. The reaction mixture was stirred at 40 °C for 2 days, cooled, and concentrated. The residue was treated with water (20 mL) and EtOAc (100 mL), and heated at 65 °C for 30 min. After cooling to room temperature, the mixture was extracted with EtOAc. The organic extract was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **265** (1.05 g, 68% yield) as an off-white solid. *m/z* = 419 (M+1).

Compound 266: Compound **265** (1.05 g, 2.51 mmol) was taken up in toluene (8 mL). Phosphorus(V) oxychloride (4 g, 26.09 mmol) was added. The mixture was heated in Biotage® Initiator™ microwave synthesizer at 100 °C for 60 min, cooled, and poured into ice. After sitting for 10 min, the mixture was extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$, dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give a mixture of ketal and ketone (600 mg). The mixture was mixed in benzene (100 mL), and treated with ethylene glycol (1 g, 16.11 mmol) and *p*-toluenesulfonic acid monohydrate (60 mg, 0.32 mmol). The mixture was refluxed for 16 h with a Dean-Stark trap, cooled to room temperature, and washed with water. The organic extract was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **266** (300 mg, 27% yield) as a light color solid. *m/z* = 437 (M+1).

Compound 267: Compound **266** (300 mg, 0.69 mmol) was taken up in THF (10 mL). Cyclobutanol (75 mg, 1.04 mmol) and NaH (60% dispersion in mineral oil, 45 mg, 1.13 mmol) were added. The reaction mixture was stirred at 60 °C for 16 h, cooled, and concentrated. The residue was neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **267** (300 mg, 92% yield) as a foam. *m/z* = 473 (M+1).

Compound 268: A mixture of compound **267** (300 mg, 0.63 mmol) was taken up in THF (6 mL), and aq. 3N HCl (3 mL, 9.0 mmol) was added. The mixture was stirred overnight at room temperature and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, filtered, and concentrated to give compound **268** (220 mg, 81 % yield) as a white solid. *m/z* = 429 (M+1).

Compound 269: Compound **268** (200 mg, 0.47 mmol) was taken up in ethyl formate (15 mL, 186 mmol). Sodium methoxide (30 wt.% solution in MeOH, 170 mg, 0.94 mmol) was added. The mixture was stirred at room temperature for 2 h, neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated to give compound **269** (215 mg, quantitative yield) as a foam. *m/z* = 457 (M+1).

Compound 270: Compound **269** (215 mg, 0.47 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (335 mg, 4.82 mmol) and acetic acid (280 mg, 4.66 mmol) were added.

The reaction mixture was stirred overnight at 50 °C, cooled, and concentrated. The residue was taken up in EtOAc and washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, filtered and concentrated to give compound **270** (210 mg, quantitative yield) as a foam. *m/z* = 454 (M+1).

Compound 271: Compound **270** (210 mg, 0.46 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (310 mg, 2.24 mmol) was added. The reaction mixture was stirred at room temperature overnight, neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **271** (70 mg, 33% yield) as a foam. *m/z* = 454 (M+1).

T112: Compound **271** (70 mg, 0.15 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin (25 mg, 0.087 mmol) in DMF (1 mL) was added. The reaction stirred at 0 °C for 2 h, and pyridine (2 mL, 24.8 mmol) was added. The mixture was heated at 60 °C for 4 h, cooled and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T112** (45 mg, 65% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.85 (s, 1H), 8.30 (ddd, J = 0.7, 1.5, 8.5 Hz, 1H), 8.17 (td, J = 0.9, 8.6 Hz, 1H), 7.97 (ddd, J = 1.4, 6.9, 8.5 Hz, 1H), 7.67 (ddd, J = 1.2, 6.9, 8.3 Hz, 1H), 5.37 (m, 1H), 2.97 (ddd, J = 0.9, 6.7, 19.0 Hz, 1H), 2.74 (ddd, J = 7.6, 11.3, 18.8 Hz, 1H), 2.60 (qd, J = 6.7, 13.3 Hz, 1H), 2.47 (m, 2H), 2.20 (m, 4H), 1.84 (m, 2H), 1.65 (m, 1H), 1.50 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 452 (M+1).

Compound 272a: Compound **266** (760 mg, 1.74 mmol) was taken up in 1,4-dioxane (8 mL). Potassium carbonate (725 mg, 5.24 mmol), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (200 mg, 0.27 mmol) and 3-fluorophenylboronic acid (365 mg, 2.61 mmol) were added. The mixture was sparged with nitrogen for 10 min, and stirred at 90 °C for 16 h. Upon cooling to room temperature, the mixture was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **272a** (510 mg, 59% yield) as a foam. *m/z* = 497 (M+1).

Compound 273a: Compound **272a** (510 mg, 1.02 mmol) was taken up in THF (10 mL), and aq. 3 N HCl (5 mL, 15.0 mmol) was added. The mixture was stirred overnight at room temperature, and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, dried over $MgSO_4$, filtered and concentrated to give compound **273a** (460 mg, 99% yield) as a foam. *m/z* = 453 (M+1).

Compound 274a: Compound **273a** (460 mg, 1.01 mmol) was taken up in ethyl formate (15 mL, 186 mmol). Sodium methoxide (30 wt.% in methanol, 200 mg, 1.11 mmol) was added. The mixture was stirred at room temperature for 2 h, neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried with $MgSO_4$, filtered and concentrated to give compound **274a** (490 mg, quantitative yield) as a foam. *m/z* = 481 (M+1).

Compound 275a: Compound **274a** (490 mg, 1.01 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (710 mg, 10.22 mmol) and acetic acid (615 mg, 10.12 mmol) were added.

The reaction mixture was stirred overnight at 50 °C, cooled and concentrated. The residue was taken up in EtOAc and washed with aq. $NaHCO_3$. The organic extract was dried over $MgSO_4$, filtered and concentrated to give compound **275a** (440 mg, 91% yield) as a foam. *m/z* = 478 (M+1).

Compound 276a: Compound **275a** (440 mg, 0.92 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (650 mg, 4.69 mmol) was added. The reaction mixture was stirred at room temperature overnight, neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **276a** (270 mg, 61% yield) as a foam. *m/z* = 478 (M+1).

T113: Compound **276a** (270 mg, 0.57 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin (90 mg, 0.31 mmol) in DMF (1 mL) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 24.8 mmol) was added, and the reaction was heated at 60 °C for 4 h. Upon cooling to room temperature, the mixture was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T113** (115 mg, 43% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.89 (s, 1H), 8.37 (ddd, J = 0.6, 1.4, 8.5 Hz, 1H), 8.19 (td, J = 0.9, 8.4 Hz, 1H), 7.99 (ddd, J = 1.4, 6.9, 8.4 Hz, 1H), 7.72 (ddd, J = 1.2, 6.9, 8.3 Hz, 1H), 7.49 (dt, J = 5.6, 8.0 Hz, 1H), 7.39 (ddd, J = 1.1, 1.6, 7.7 Hz, 1H), 7.33 (ddd, J = 1.5, 2.5, 9.2 Hz, 1H), 7.20 (ddt, J = 1.1, 2.6, 8.4 Hz, 1H), 3.06 (m, 2H), 2.64 (qd, J = 6.7, 13.3 Hz, 1H), 2.32 (dt, J = 2.7, 12.7 Hz, 1H), 2.22 (tdd, J = 3.2, 5.9, 13.6 Hz, 1H), 1.87 (m, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 476 (M+1).

Compound 272b: Compound **266** (780 mg, 1.79 mmol) was taken up in 1,4-dioxane (8 mL). Potassium carbonate (740 mg, 5.35 mmol), [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (210 mg, 0.29 mmol) and 4-fluorophenylboronic acid (375 mg, 2.68 mmol) were added. The mixture was sparged with nitrogen for 10 min and stirred at 90 °C for 16 h. Upon cooling to room temperature, the mixture was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **272b** (650 mg, 73% yield) as a foam. *m/z* = 497 (M+1).

Compound 273b: Compound **272b** (650 mg, 1.31 mmol) was taken up in THF (10 mL), and aq. 3 N HCl (5 mL, 15.0 mmol) was added. The mixture was stirred overnight at room temperature and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$ and extracted with EtOAc. The organic extract was washed with water, dried over $MgSO_4$, filtered and concentrated to give compound **273b** (595 mg, quantitative yield) as a foam. *m/z* = 453 (M+1).

Compound 274b: Compound **273b** (595 mg, 1.31 mmol) was taken up in ethyl formate (15 mL, 186 mmol). Sodium methoxide (30 wt.% in methanol, 230 mg, 1.28 mmol) was added. The mixture was stirred at room temperature for 2 h, neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried over $MgSO_4$, filtered and concentrated to give compound **274b** (620 mg, 98% yield) as a foam. *m/z* = 481 (M+1).

Compound 275b: Compound **274b** (620 mg, 1.29 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (900 mg, 12.95 mmol) and acetic acid (780 mg, 12.98 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled and concentrated. The residue was taken up in EtOAc and washed with aq. $NaHCO_3$. The organic extract was dried over $MgSO_4$, filtered and concentrated to give compound **275b** (540 mg, 88% yield) as a foam. *m/z* = 478 (M+1).

Compound 276b: Compound **275b** (540 mg, 1.13 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (650 mg, 4.70 mmol) was added. The reaction mixture was stirred at room temperature overnight, neutralized by the addition of aq. sat. KH_2PO_4, and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **276b** (290 mg, 54% yield) as a foam. *m/z* = 478 (M+1).

T114: Compound **276b** (290 mg, 0.61 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin (96 mg, 0.34 mmol) in DMF (1 mL) was added, and the mixture was stirred at 0 °C for 2 h. Pyridine (2 ml, 24.8 mmol) was added. The reaction was heated at 60 °C for 4 h, cooled and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T114** (125 mg, 43% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.89 (s, 1H), 8.37 (ddd, J = 0.6, 1.4, 8.5 Hz, 1H), 8.19 (td, J = 0.9, 8.5 Hz, 1H), 7.99 (ddd, J = 1.4, 6.9, 8.5 Hz, 1H), 7.71 (ddd, J = 1.2, 6.9, 8.3 Hz, 1H), 7.63 (m, 2H), 7.20 (m, 2H), 3.07 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.32 (dt, J = 2.8, 12.8 Hz, 1H), 2.22 (tdd, J = 3.1, 6.0, 13.8 Hz, 1H), 1.86 (m, 1H), 1.59 (s, 3H), 1.35 (d, J = 6.7 Hz, 3H); *m/z* = 476 (M+1).

Compound 277: A mixture of compound **170d** (0.99 g, 1.94 mmol) and selenium dioxide (0.44 g, 3.96 mmol) in 1,4-dioxane (20 mL) was heated at 100 °C under nitrogen for 1 h. The mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **277** (0.87 g, 85% yield) as a light yellow foamy solid. *m/z* = 524 (M+1).

Compound 278: A solution of compound **277** (0.46 g, 0.88 mmol) in EtOH (10 mL) was treated with $NaBH_4$ (0.033 g, 0.87 mmol). The mixture was stirred at room temperature under nitrogen for 16 h and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **278** (0.45 g, 98% yield) as an off-white foamy solid. *m/z* = 526 (M+1).

Compound 279: To a solution at 0 °C of compound **278** (0.45 g, 0.86 mmol) in CH_2Cl_2 (9 mL) was added a solution of (diethylamino)sulfur trifluoride (0.28 g, 1.74 mmol) in CH_2Cl_2 (2 mL). The resultant blue solution was stirred at 0 °C for 2 h and then partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **279** (0.27 g, 60% yield) as light yellow foamy solid. *m/z* = 528 (M+1).

Compound 280: A solution of compound **279** (0.27 g, 0.51 mmol) and aq. 3 N HCl (1.7 mL, 5.1 mmol) in MeOH (5 mL) was stirred at room temperature overnight. The mixture was concentrated,

cooled, basified with aq. 10% NH_4OH, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **280** (0.25 g, quantitative yield) as a light yellow foamy solid. *m/z* = 484 (M+1).

Compound 281: A solution at room temperature of compound **280** (0.25 g, 0.51 mmol) in ethyl formate (10 mL, 124 mmol) was treated with sodium methoxide (30 wt.% in methanol, 0.30 mL, 1.60 mmol). The mixture was stirred for 2 h and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **281** (0.25 g, 95% yield) as an orange foamy solid. *m/z* = 512 (M+1).

Compound 282: A solution of compound **281** (0.25 g, 0.48 mmol) and acetic acid (0.28 mL, 4.89 mmol) in EtOH (5 mL) was treated with hydroxylamine hydrochloride (0.051 g, 0.73 mmol). The mixture was stirred at 60 °C under nitrogen for 2 h at room temperature overnight and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give compound **282** (0.23 g, 92% yield) as an orange-brown foamy solid. *m/z* = 509 (M+1).

Compound 283: A mixture of compound **282** (0.23 g, 0.45 mmol) and potassium carbonate (0.31 g, 2.24 mmol) in MeOH (5 mL) was stirred at room temperature under nitrogen for 16 h and then filtered. The filtrate was concentrated, and the residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **283** (0.14 g, 61% yield) as a light yellow foamy solid. *m/z* = 509 (M+1).

T115: To a stirring solution at 0 °C under nitrogen of compound **283** (0.14 g, 0.28 mmol) in degassed DMF (5 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (0.043 g, 0.15 mmol). After stirring the mixture for 30 min, pyridine (0.22 mL, 2.72 mmol) was added. The ice-bath was removed, and the mixture was heated at 60 °C for 4 h. Upon cooling to room temperature, the mixture was concentrated, and the residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T115** (0.071 g, 51% yield) as a light yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.64 (dd, J = 0.8, 8.4 Hz, 1H), 8.16 (m, 2H), 7.79 (ddd, J = 1.4, 6.8, 8.5 Hz, 1H), 7.64 (ddd, J = 1.3, 6.8, 8.3 Hz, 1H), 7.50 (m, 2H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.24 (m, 1H), 5.75 (d, J = 46.9 Hz, 2H), 2.90 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.32 (dt, J = 2.7, 12.8 Hz, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 1.61 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 507 (M+1).

Compound 284: A solution of compound **278** (0.815 g, 1.55 mmol) and aq. 3 N HCl (5.2 mL, 15.6 mmol) in MeOH (15 mL) was stirred at room temperature overnight. The mixture was concentrated; the residue was carefully partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **284** (0.69 g, 92% yield) as a light yellow foamy solid. *m/z* = 482 (M+1).

Compound 285: To a stirring solution at room temperature of compound **284** (0.69 g, 1.43 mmol) in ethyl formate (10 mL, 124 mmol) was added sodium methoxide (30 wt.% solution in MeOH, 0.81 mL, 4.32 mmol). The mixture was stirred for 2 h and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **285** (0.707 g, 97% yield) as an orange foamy solid. *m/z* = 510 (M+1).

Compound 286: A solution of compound **285** (0.707 g, 1.39 mmol) and acetic acid (0.80 mL, 13.99 mmol) in EtOH (25 mL) was treated with hydroxylamine hydrochloride (0.14 g, 2.01 mmol). The mixture was stirred at 60 °C under nitrogen for 2 h then at room temperature overnight. The mixture was concentrated; the residue was partitioned between aq. sat. $NaHCO_3$ solution (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **286** (0.43 g, 61% yield) as an orange foamy solid. *m/z* = 507 (M+1).

Compound 287: A mixture of compound **286** (0.43 g, 0.85 mmol) and potassium carbonate (0.62 g, 4.49 mmol) in MeOH (20 mL) was stirred at room temperature under nitrogen overnight. The mixture was concentrated; the residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 75% EtOAc in hexanes) to give compound **287** (0.30 g, 70% yield) as a yellow foamy solid. *m/z* = 507 (M+1).

T116: To a stirring solution at 0 °C under nitrogen of compound **287** (0.30 g, 0.59 mmol) in benzene (10 mL) was added in one portion DDQ (0.15 g, 0.66 mmol). The reaction was heated at 80 °C for 0.5 h. The mixture was cooled and concentrated. The residue was partitioned between aq. sat. Na_2CO_3 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 25% to 75% EtOAc in hexanes) to give compound **T116** (0.047 g, 16% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.91 (s, 1H), 8.73 (dd, J = 1.3, 8.6 Hz, 1H), 8.59 (s, 1H), 8.37 (m, 1H), 7.88 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.51 (m, 2H), 7.34 (dt, J = 1.1, 7.5 Hz, 1H), 7.24 (m, 1H), 2.91 (m, 2H), 2.65 (qd, J = 6.7, 13.3 Hz, 1H), 2.32 (dt, J = 2.8, 12.8 Hz, 1H), 2.19 (m, 1H), 1.87 (m, 1H), 1.61 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 503 (M+1).

Impure **compound 288** (0.075 g) was also obtained as a dark yellow solid from the column. The sample was purified again by flash chromatography (silica gel, eluting with 5% MeOH in $CHCl_3$) to give compound **288** (0.028 g, 9% yield from compound **287**) as a light yellow foamy solid which was still impure. *m/z* = 505 (M+1).

T117: A mixture of compound **288** (0.028 g, 0.055 mmol) and sodium acetate (50 mg, 0.61 mmol) in acetic anhydride (2 mL) was stirred at room temperature overnight. The mixture was concentrated and purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give **T117** (0.015 g, 50% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s,

1H), 8.64 (dd, J = 1.4, 8.7 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.63 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 7.50 (m, 2H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.24 (m, 1H), 5.48 (s, 2H), 2.91 (m, 2H), 2.65 (qd, J = 6.7, 13.3 Hz, 1H), 2.31 (dt, J = 2.7, 12.8 Hz, 1H), 2.21 (s, 3H), 2.19 (m, 1H), 1.87 (m, 1H), 1.60 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 547 (M+1).

Compound 289: To a stirring solution of compound **4** (30.37 g, assume 145.2 mmol) and pyridinium *p*-toluenesulfonate (3.60 g, 14.32 mmol) in CH_2Cl_2 (400 mL) was added dropwise 3,4-dihydro-2*H*-pyran (14.6 mL, 160.0 mmol) at room temperature under nitrogen. The mixture was stirred overnight and concentrated. The residue was partitioned between EtOAc (400 mL) and aq. sat. $NaHCO_3$ (400 mL). The organic extract was washed with aq. sat. KH_2PO_4 (400 mL), brine (400 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give compound **289** (26.86 g, 66% yield) as a viscous colorless oil. *m/z* = 279 (M+1).

Compound 290: To a stirring solution at room temperature under nitrogen of compound **289** (10.16 g, 36.49 mmol) in benzene (145 mL) was added portionwise potassium *tert*-butoxide (4.09 g, 36.45 mmol) over 30 min. After addition, the resulting dark suspension was heated at 60 °C for 30 min, cooled to 0 °C, and treated with dropwise addition of iodomethane (6.8 mL, 109.2 mmol). The mixture was slowly allowed to warm to room temperature overnight and quenched with aq. sat. KH_2PO_4 (200 mL). The organic extract was washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give compound **290** (8.60 g, 80% yield) as a viscous light yellow oil. *m/z* = 293 (M+1).

Compound 291: A solution of compound **290** (10.63 g, 36.35 mmol) and pyridinium *p*-toluenesulfonate (0.91 g, 3.62 mmol) in EtOH (100 mL) was refluxed under nitrogen overnight. The mixture was cooled, and concentrated. The residue was partitioned between aq. 1 N HCl (50 mL) and EtOAc (50 mL). The organic extract was washed with aq. sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give compound **291** (6.32 g, 83% yield) as a white waxy solid. *m/z* = 209 (M+1).

Compound 292: A solution of compound **291** (6.32 g, 30.34 mmol), ethylene glycol (17 mL, 305 mmol) and *p*-toluenesulfonic acid monohydrate (0.58 g, 3.05 mmol) in benzene (100 mL) was refluxed with Dean-Stark conditions trap overnight. The mixture was cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. $NaHCO_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give compound **292** (7.68 g, quantitative yield) as a yellow waxy solid. *m/z* = 253 (M+1).

Compound 293: A mixture of compound **292** (1.39 g, 5.51 mmol) and 20 wt.% palladium hydroxide on carbon (0.30 g) in MeOH (60 mL) was hydrogenated (1 atm) at room temperature for 7 days. The catalyst was removed by filtration, and the filtrate was concentrated to give a mixture of ketal and ketone (1.42 g). The mixture was dissolved in benzene (100 mL), and treated with ethylene glycol

(3.1 mL, 55.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.11 g, 0.58 mmol). The mixture was refluxed with Dean-Stark trap for 4 h, and then cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. $NaHCO_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated. The residue was purified by flash chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give compound **293** (0.92 g, 66% yield) as a gummy white solid. *m/z* = 237 (M-OH).

Compound 294: Compound **293** (0.92 g, 3.62 mmol) in CH_2Cl_2 (50 mL) was treated with $MgSO_4$ (0.44 g, 3.66 mmol) and pyridinium dichromate (6.82 g, 18.13 mmol). After stirring the mixture at room temperature under nitrogen for 16 h, additional amount of pyridinium dichromate (3.41 g, 9.06 mmol) was added. The mixture was stirred for a second night and concentrated. The residue was diluted with Et_2O (50 mL), stirred at room temperature for 2 h, and filtered through a pad of Celite®. The filtrate was concentrated to give compound **294** (0.81 g, 88% yield) as an off-white gummy solid. *m/z* = 253 (M+1).

Compound 295: A solution of compound **294** (0.61 g, 2.43 mmol), 2-fluorobenzaldehyde (0.33 g, 2.66 mmol) and potassium fluoride (40 wt.% on alumina, 0.53 g, 3.65 mmol) in EtOH (8 mL) was stirred at room temperature under nitrogen overnight. The mixture was filtered through a pad of Celite®, and the filtrate was concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (100 mL) and EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 5% EtOAc in CH_2Cl_2) to give compound **295** (0.59 g, 68% yield) as a light yellow waxy solid. *m/z* = 359 (M+1).

Compound 296a: A mixture of compound **295** (0.59 g, 1.65 mmol), 4-quinolinecarboximidamide hydrochloride (0.51 g, 2.46 mmol) and potassium carbonate (0.68 g, 4.92 mmol) in EtOH (16 mL) was refluxed under nitrogen overnight. The mixture was cooled, and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved in CH_2Cl_2 (50 mL), and treated with manganese dioxide (88%, 0.81 g, 8.20 mmol). The mixture was stirred at room temperature overnight and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **296a** (0.62 g, 74% yield) as a light yellow foamy solid. *m/z* = 510 (M+1).

Compound 297a: A solution of compound **296a** (0.62 g, 1.22 mmol) and aq. 3 N HCl (2.0 mL, 6.0 mmol) in MeOH (12 mL) was stirred at room temperature overnight, and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$,filtered and concentrated to give compound **297a** (0.60 g, quantitative yield) as an off-white foamy solid. *m/z* = 466 (M+1).

Compound 298a: A solution of compound **297a** (all from the last step) in ethyl formate (10 mL, 124 mmol) was treated with sodium methoxide (30 wt.% solution in methanol, 0.70 mL, 3.73 mmol) at room temperature under nitrogen. The mixture was stirred for 2 h, and then partitioned between EtOAc

(50 mL) and aq. sat. KH_2PO_4 solution (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **298a** (0.58 g, 96% yield) as a tan foamy solid. *m/z* = 494 (M+1).

Compound 299a: To a solution of compound **298a** (0.58 g, 1.17 mmol) in EtOH (12 mL) was added acetic acid (0.70 mL, 12.23 mmol) and hydroxylamine hydrochloride (0.13 g, 1.87 mmol). The mixture was stirred at 60 °C under nitrogen for 2 h, at room temperature overnight, and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **299a** (0.56 g, 97% yield) as light yellow foamy solid. *m/z* = 491 (M+1).

Compound 300a: A mixture of compound **299a** (0.56 g, 1.14 mmol) and potassium carbonate (0.79 g, 5.72 mmol) in MeOH (11 mL) was stirred at room temperature under nitrogen for 16 h. After filtration, the filtrate was concentrated, and the residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **300a** (0.41 g, 73% yield) as a light yellow foamy solid. *m/z* = 491 (M+1).

T118: To a stirring solution at 0 °C under nitrogen of compound **300a** (0.41 g, 0.84 mmol) in degassed DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.13 g, 0.45 mmol) in DMF (2 mL). After stirring the mixture for 30 min, pyridine (0.7 mL, 8.67 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **T118** (0.22 g, 54% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 4.5 Hz, 1H), 8.93 (s, 1H), 8.69 (dd, J = 0.8, 8.4 Hz, 1H), 8.21 (dd, J = 0.4, 8.4 Hz, 1H), 8.01 (d, J = 4.6 Hz, 1H), 7.77 (ddd, J = 1.2, 6.6, 7.9 Hz, 1H), 7.63 (tdd, J = 1.0, 6.8, 7.8 Hz, 1H), 7.50 (m, 2H), 7.33 (dt, J = 1.0, 7.5 Hz, 1H), 7.24 (m, 1H), 2.91 (dd, J = 4.7, 8.6 Hz, 2H), 2.39 (dd, J = 2.9, 12.2 Hz, 1H), 2.02 (m, 2H), 1.65 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H); *m/z* = 489 (M+1).

Compound 296b: A mixture of compound **295** (0.54 g, 1.51 mmol), 2-methyl-4-quinolinecarboximidamide hydrochloride (0.42 g, 1.89 mmol) and potassium carbonate (0.63 g, 4.56 mmol) in EtOH (5 mL) was refluxed under nitrogen overnight. The mixture was cooled and concentrated. The residue was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the dihydropyrimidine. The crude product was dissolved into CH_2Cl_2 (50 mL) and treated with manganese dioxide (88%, 0.75 g, 7.59 mmol). The mixture was stirred at room temperature overnight and filtered. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **296b** (0.62 g, 78% yield) as a light yellow foamy solid. *m/z* = 524 (M+1).

Compound 297b: A solution of compound **296b** (0.24 g, 0.45 mmol) and aq. 3 N HCl (1.5 mL, 4.5 mmol) in MeOH (10 mL) was stirred at room temperature overnight and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **297b** (0.22 g, quantitative yield) as an off-white foamy solid. *m/z* = 480 (M+1).

Compound 298b: A solution of compound **297b** (0.22 g, 0.45 mmol) in ethyl formate (10 mL, 124 mmol) was treated with sodium methoxide (30 wt.% solution in methanol, 0.26 mL, 1.39 mmol) at room temperature under nitrogen. The mixture was stirred for 2 h and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **298b** (0.20 g, 86% yield) as a yellow foamy solid. *m/z* = 508 (M+1).

Compound 299b: To a solution of compound **298b** (0.20 g, 0.39 mmol) in EtOH (40 mL) was added acetic acid (0.23 mL, 4.02 mmol) and hydroxylamine hydrochloride (0.042 g, 0.60 mmol). The mixture was stirred at 60 °C under nitrogen for 2 h at room temperature overnight and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **299b** (0.18 g, 91% yield) as a tan foamy solid. *m/z* = 505 (M+1).

Compound 300b: A mixture of compound **299b** (0.18 g, 0.36 mmol) and potassium carbonate (0.24 g, 1.74 mmol) in MeOH (10 mL) was stirred at room temperature under nitrogen for 16 h. After filtration, the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 30% to 50% EtOAc in hexanes) to give compound **300b** (0.088 g, 49% yield) as a light yellow foamy solid. *m/z* = 505 (M+1).

T119: To a stirring solution at 0 °C under nitrogen of compound **300b** (0.088 g, 0.17 mmol) in degassed DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.027 g, 0.094 mmol) in DMF (1 mL). After stirring the mixture for 30 min, pyridine (0.14 mL, 1.73 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 10% EtOAc in CH_2Cl_2) to give compound **T119** (0.031 g, 36% yield) as a light yellow foamy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.57 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.73 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.51 (m, 3H), 7.33 (dt, J = 1.1, 7.5 Hz, 1H), 7.25 (m, 1H), 2.90 (dd, J = 4.6, 8.4 Hz, 2H), 2.85 (s, 3H), 2.39 (dd, J = 2.8, 12.1 Hz, 1H), 2.03 (m, 2H), 1.65 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H); *m/z* = 503 (M+1).

Compound 301: A mixture of compound **260b** (0.90 g, 1.80 mmol) and selenium dioxide (0.40 g, 3.60 mmol) in 1,4-dioxane (18 mL) was heated at 100 °C under nitrogen for 1 h. The mixture was

cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated to give compound **301** (0.92 g, 99% yield) as an off-white solid. *m/z* = 514 (M+1).

Compound 302: A solution of compound **301** (0.92 g, 1.79 mmol) in EtOH (18 mL) was treated with $NaBH_4$ (0.068 g, 1.79 mmol) at room temperature. After stirring under nitrogen for 1 h, the mixture was concentrated, and the residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give compound **302** (0.92 g, quantitative yield) as a tan foamy solid. *m/z* = 516 (M+1).

Compound 303: To a solution of compound **302** (0.92 g, 1.78 mmol) in CH_2Cl_2 (20 mL) was added a solution of diethylaminosulfur trifluoride (0.58 g, 3.60 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The resultant blue solution was stirred at 0 °C for 2 h and then partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give compound **303** (0.47 g, 51% yield) as a light yellow foamy solid. *m/z* = 518 (M+1).

Compound 304: A solution of compound **303** (0.47 g, 0.91 mmol) and aq. 3 N HCl (1.5 mL, 4.5 mmol) in MeOH (45 mL) was stirred at room temperature overnight and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **304** (0.43 g, quantitative yield) as a tan foamy solid. *m/z* = 474 (M+1).

Compound 305: A solution of compound **304** (0.43 g, 0.91 mmol) in ethyl formate (10 mL, 124 mmol) was treated with sodium methoxide (30 wt.% solution in MeOH, 0.51 mL, 2.72 mmol) at room temperature. The mixture was stirred for 2 h and then partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **305** (0.47 g) as a dark yellow oil. *m/z* = 502 (M+1).

Compound 306: A solution of compound **305** (all from the last step) and acetic acid (0.51 mL, 8.92 mmol) in EtOH (25 mL) was treated with hydroxylamine hydrochloride (0.10 g, 1.44 mmol). The mixture was stirred at 60 °C under nitrogen for 2 h at room temperature overnight and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give compound **306** (0.40 g, 88% yield) as an orange-brown foamy solid. *m/z* = 499 (M+1).

Compound 307: A mixture of compound **306** (0.40 g, 0.80 mmol) and potassium carbonate (0.56 g, 4.05 mmol) in MeOH (8 mL) was stirred at room temperature under nitrogen for 16 h. After filtration, the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give compound **307** (0.23 g, 58% yield) as light yellow foamy solid. *m/z* = 499 (M+1).

T120: To a stirring solution of compound **307** (0.23 g, 0.46 mmol) in degassed DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.071 g, 0.25 mmol) in DMF (2 mL) at 0 °C under nitrogen. After stirring the mixture for 30 min, pyridine (0.37 mL, 4.59 mmol) was added.

The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 30% EtOAc in hexanes) to give compound **T120** (0.12 g, 52% yield) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.74 (dd, J = 0.8, 8.6 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 1.1 Hz, 1H), 7.78 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.62 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 5.73 (d, J = 46.8 Hz, 2H), 5.63 (tt, J = 2.7, 6.1 Hz, 1H), 2.91 (dd, J = 6.3, 18.9 Hz, 1H), 2.66 (m, 2H), 2.18 (m, 2H), 2.03 (m, 2H), 1.86 (m, 5H), 1.68 (m, 2H), 1.52 (s, 3H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 497 (M+1).

Compound 308: Compound **9** (1.25 g, 4.22 mmol) was taken up in EtOH (15 mL). 8-fluoroquinoline-4-carboximidamide hydrochloride (0.95 g, 4.21 mmol) and potassium carbonate (1.2 g, 8.68 mmol) were added. The reaction mixture was stirred at 40 °C for 2 days, cooled and concentrated. The residue was mixed with water (20 mL) and EtOAc (100 mL) and heated at 65 °C for 30 min. After cooled to room temperature, the organic extract was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **308** (1.6 g, 87% yield) as an off-white solid. *m/z* = 436 (M+1).

Compound 309: To a solution of compound **308** (1.25 g, 2.87 mmol) in toluene (8 mL) was added phosphorus(V) oxychloride (4.4 g, 28.70 mmol) at room temperature. The mixture was heated in Biotage® Initiator™ microwave synthesizer at 100 °C for 60 min, cooled to room temperature, and poured into ice. The mixture was stirred for 30 min and extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to give a mixture of ketal and ketone. The crude product was mixed in benzene (100 mL) and treated with ethylene glycol (1.8 g, 29.00 mmol) and *p*-toluenesulfonic acid monohydrate (100 mg, 0.52 mmol). The mixture was refluxed for 16 h with a Dean-Stark trap, cooled to room temperature, and washed with water. The organic extract was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **309** (950 mg, 73% yield) as a light color solid. *m/z* = 454 (M+1).

Compound 310: Compound **309** (950 mg, 2.09 mmol) was taken up in THF (10 mL). Cyclopentanol (1 g, 11.61 mmol) and sodium hydride (60% dispersion in mineral oil (400 mg, 10 mmol) were added. The mixture was stirred at 60 °C for 16 h, cooled, and concentrated. The residue was neutralized by the addition of aq. sat. KH_2PO_4 and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **310** (420 mg, 40% yield) as a light color solid. *m/z* = 504 (M+1).

Compound 311: A mixture of compound **310** (420 mg, 0.83 mmol) was taken up in THF (10 mL), and aq. 3 N HCl (5 mL, 15 mmol) was added. The mixture was stirred overnight at room temperature and concentrated. The residue was neutralized with aq. sat. $NaHCO_3$ and extracted with

EtOAc. The organic extract was washed with water, dried over $MgSO_4$, filtered and concentrated to give compound **311** (385 mg, quantitative yield) as a foam. *m/z* = 460 (M+1).

Compound 312: To a mixture of compound **311** (385 mg, 0.83 mmol) in ethyl formate (15 mL, 186.5 mmol) was added sodium methoxide (30 wt.% in methanol, 160 mg, 0.89 mmol). The mixture was stirred at room temperature for 2 h, neutralized with aq. KH_2PO_4, and extracted with EtOAc. The organic extract was dried over $MgSO_4$, filtered and concentrated to give compound **312** (405 mg, quantitative yield) as a foam. *m/z* = 488 (M+1).

Compound 313: Compound **312** (405 mg, 0.83 mmol) was dissolved in EtOH (15 mL). Hydroxylamine hydrochloride (570 mg, 8.20 mmol) and AcOH (500 mg, 8.32 mmol) were added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in EtOAc and washed with aq. $NaHCO_3$. The organic extract was dried over $MgSO_4$, filtered and concentrated to give compound **313** (350 mg, 87% yield) as a foam. *m/z* = 485 (M+1).

Compound 314: Compound **313** (350 mg, 0.72 mmol) was dissolved in MeOH (10 mL). Potassium carbonate (500 mg, 3.62 mmol) was added. After stirring at room temperature overnight, the reaction mixture was neutralized by the addition of aq. sat. KH_2PO_4 and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **314** (250 mg, 71% yield) as a foam. *m/z* = 485 (M+1).

T121: Compound **314** (250 mg, 0.51 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (91 mg, 0.57 mmol) in CH_2Cl_2 (1 mL) was added. The reaction was stirred at 0 °C for 2 h, and pyridine (2 mL, 24.8 mmol) was added. The ice-bath was removed. The reaction mixture heated at 60 °C for 4 h, cooled and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **T121** (155 mg, 62% yield) as a foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, J = 4.4 Hz, 1H), 8.86 (s, 1H), 8.61 (td, J = 1.1, 8.6 Hz, 1H), 8.06 (d, J = 4.4 Hz, 1H), 7.56 (ddd, J = 5.3, 7.7, 8.6 Hz, 1H), 7.47 (ddd, J = 1.3, 7.7, 10.3 Hz, 1H), 5.61 (tt, J = 2.7, 6.1 Hz, 1H), 2.91 (ddd, J = 1.1, 6.8, 18.8 Hz, 1H), 2.66 (m, 2H), 2.18 (m, 2H), 1.83 (m, 9H), 1.51 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H); *m/z* = 483 (M+1).

Compound 315: A mixture of compound **296b** (0.36 g, 0.69 mmol) and selenium dioxide (0.15 g, 1.35 mmol) in 1,4-dioxane (10 mL) was heated at 100 °C under nitrogen for 15 min. The mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give compound **315** (0.32 g, 87% yield) as an off-white foamy solid. *m/z* = 538 (M+1).

Compound 316: A solution of compound **315** (0.32 g, 0.60 mmol) in EtOH (50 mL) was treated with $NaBH_4$ (0.023 g, 0.61 mmol) at room temperature. After stirring under nitrogen for 1 h, the mixture was cooled to 0 °C, quenched with aq. sat. KH_2PO_4 (50 mL), and concentrated. The residue was extracted with EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$,

filtered and concentrated to give compound **316** (0.28 g, 87% yield) as a light yellow foamy solid. *m/z* = 540 (M+1).

Compound 317: To a solution of compound **316** (0.28 g, 0.52 mmol) in CH_2Cl_2 (5 mL) was added a solution of diethylaminosulfur trifluoride (0.17 g, 1.05 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The resultant blue solution was stirred at 0 °C for 2 h and partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 30% EtOAc in hexanes) to give compound **317** (0.16 g, 57% yield) as an off-white foamy solid. *m/z* = 542 (M+1).

Compound 318: A solution of compound **317** (0.16 g, 0.30 mmol) and aq. 3 N HCl (1 mL, 3 mmol) in MeOH (10 mL) was stirred at room temperature overnight and concentrated. The residue was cooled, basified with aq. 10% NH_4OH, and extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **318** (0.15 g, quantitative yield) as a yellow oil. *m/z* = 498 (M+1).

Compound 319: A solution of compound **318** (0.15 g, 0.30 mmol) in ethyl formate (10 mL, 124 mmol) was treated with sodium methoxide (30 wt.% solution in MeOH, 0.16 mL, 0.86 mmol) at room temperature. After stirring for 2 h, the mixture was partitioned between EtOAc (50 mL) and aq. sat. KH_2PO_4 (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **319** (0.14 g, 88% yield) as an orange foamy solid. *m/z* = 526 (M+1).

Compound 320: A solution of compound **319** (0.14 g, 0.26 mmol) and acetic acid (0.15 mL, 2.62 mmol) in EtOH (20 mL) was treated with hydroxylamine hydrochloride (0.027 g, 0.39 mmol). The mixture was stirred at 60 °C under nitrogen for 2 h at room temperature overnight and concentrated. The residue was partitioned between aq. sat. $NaHCO_3$ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give compound **320** (0.13 g, 93% yield) as an orange foamy solid. *m/z* = 523 (M+1).

Compound 321: A mixture of compound **320** (0.13 g, 0.25 mmol) and potassium carbonate (0.17 g, 1.23 mmol) in MeOH (5 mL) was stirred at room temperature under nitrogen for 16 h. After filtration, the filtrate was concentrated. The residue was carefully partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **321** (0.11 g, 85% yield) as light yellow foamy solid. *m/z* = 523 (M+1).

T122: To a stirring solution of compound **321** (0.11 g, 0.21 mmol) in degassed DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.034 g, 0.12 mmol) in DMF (1 mL) at 0 °C under nitrogen. After stirring the mixture for 30 min, pyridine (0.17 mL, 2.11 mmol) was added. The ice-bath was removed. The mixture was heated at 60 °C for 4 h, cooled, and concentrated. The residue was partitioned between aq. sat. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 25% EtOAc in hexanes) to give **T122** (0.057 g, 52% yield) as a light yellow foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.63 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.16 (m, 2H), 7.79 (ddd, *J* = 1.4, 6.8, 8.4 Hz, 1H), 7.64 (ddd, *J* = 1.6, 6.8, 8.3 Hz, 1H), 7.50 (m, 2H), 7.33

(dt, J = 1.1, 7.5 Hz, 1H), 7.23 (m, 1H), 5.75 (d, J = 46.8 Hz, 2H), 2.92 (dd, *J* = 4.7, 8.5 Hz, 2H), 2.40 (dd, *J* = 2.8, 12.1 Hz, 1H), 2.01 (m, 2H), 1.66 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H); *m/z* = 521 (M+1).

Compound 322: A solution of compound **277** (530 mg, 1.01 mmol) in anhydrous THF (15 ml) was cooled to 0 °C under nitrogen. Methylmagnesium bromide (3.0 M solution in Et_2O, 0.67 mL, 2.01 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 4 h and poured into aq. sat. NH_4Cl. The aqueous mixture was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **322** (432 mg, 79% yield) as a yellow glass. *m/z* = 540 (M+1).

Compound 323: A solution of compound **322** (432 mg, 0.80 mmol) in CH_2Cl_2 (20 mL) was treated with manganese dioxide (88%, 395 mg, 4.00 mmol) at room temperature. After stirring under nitrogen for 24 h, the mixture was filtered through a pad of Celite® and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give compound **323** (388 mg, 90% yield) as a clear, viscous oil. *m/z* = 538 (M+1).

Compound 324: To suspension of methyltriphenylphosphonium bromide (1.38 g, 3.86 mmol) in anhydrous THF (30 mL) under nitrogen was added portionwise with stirring potassium *t*-butoxide (434 mg, 3.87 mmol) at 0 °C. After addition was complete, the mixture was stirred at room temperature for 2 h and cooled to 0 °C again. A solution of compound **323** (520 mg, 0.967 mmol) in anhydrous THF (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 21 h. The mixture was diluted with water and extracted with EtOAc (2 × 60 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 10% EtOAc in hexanes) to give compound **324** (478 mg, 92% yield) as a viscous oil. *m/z* = 536 (M+1).

Compound 325: A solution of compound **324** (477 mg, 0.890 mmol) in MeOH (15 mL) and EtOAc (15 mL) was treated with 10% Pd/C (50 mg) and the reaction mixture was stirred under 1 atm hydrogen at room temperature for 22 h. The catalyst was removed by filtered through a pad of Celite® and the filtrate was concentrated. The residue was purified by flash chromatography (silica gel, eluting with 20% EtOAc in hexanes) to give compound **325** (333 mg, 70% yield) as a white glass. *m/z* = 538 (M+1).

Compound 326: A solution of compound **325** (403 mg, 0.749 mmol) in THF (25 mL) was treated with aq. 3 N HCl (2.50 mL, 7.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo* and the residue was cooled to 0 °C, neutralized cautiously with aq. sat. $NaHCO_3$, and extracted with EtOAc. The organic extract was washed with water, brine, dried over $MgSO_4$, filtered and concentrated to give compound **326** (370 mg, quantitative yield) as a clear, viscous oil. *m/z* = 494 (M+1).

Compound 327: A solution of compound **326** (390 g, 0.790 mmol) in ethyl formate (12 mL, 149 mmol) was cooled to 0 °C and treated dropwise with sodium methoxide (5.4 M solution in MeOH, 0.73 ml, 3.94 mmol). The cold bath was removed and the reaction mixture was stirred at room temperature for

18 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to give compound **327** (384 mg, 93% yield) as a yellow glass. *m/z* = 522 (M+1).

Compound 328: A solution of compound **327** (382 mg, 0.732 mmol) in glacial acetic acid (0.43 mL, 7.52 mmol) and EtOH (7 mL) was treated with hydroxylamine hydrochloride (76 mg, 1.09 mmol). The reaction mixture was stirred under nitrogen at 60 °C for 4 h and at room temperature for 20 h. The solvent was removed *in vacuo* and the residue was cautiously partitioned between aq. 10% NH_4OH and EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a pale yellow glass (351 mg), which was trituration with MeOH to give compound **328** (237 mg, 62% yield) as a light yellow crystalline solid. *m/z* = 519 (M+1).

Compound 329: A suspension of compound **328** (237 mg, 0.456 mmol) and potassium carbonate (187 mg, 1.35 mmol) in MeOH (15 mL) was stirred under nitrogen at room temperature for 19 h and heated at 50 °C for 1 h. The reaction mixture was concentrated and the residue was partitioned between water and Et_2O. The aqueous phase was cooled in an ice-water bath and neutralized with aq. sat. KH_2PO_4. The neutralized aqueous mixture was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 40% EtOAc in hexanes) to give compound **329** (176 mg, 74% yield) as a white glass. *m/z* = 519 (M+1).

T123: A solution of compound **329** (176 mg, 0.339 mmol) in anhydrous DMF (4 mL) was cooled to 0 °C under nitrogen, and treated dropwise with a solution of 1,3-dibromo-5,5-dimethylhydantoin (53 mg, 0.185 mmol) in anhydrous DMF (1 mL). After stirring at 0 °C for 45 min, anhydrous pyridine (0.27 mL, 3.39 mmol) was added. The cold bath was removed, and the reaction mixture was heated at 60 °C for 4 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc and aq. sat. KH_2PO_4. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 40% EtOAc in hexanes) to give compound **T123** (126 mg, 72% yield) as an off-white glass. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.51 (dd, J = 1.3, 8.6 Hz, 1H), 8.15 (dd, J = 0.8, 8.4 Hz, 1H), 7.86 (s, 1H), 7.72 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.52 (m, 3H), 7.33 (dt, J = 1.1, 7.6 Hz, 1H), 7.23 (m, 1H), 3.36 (hept, J = 7.0 Hz, 1H), 2.89 (m, 2H), 2.64 (qd, J = 6.7, 13.4 Hz, 1H), 2.31 (dt, J = 2.8, 12.8 Hz, 1H), 2.18 (m, 1H), 1.86 (m, 1H), 1.60 (s, 3H), 1.46 (d, J = 6.9 Hz, 6H), 1.34 (d, J = 6.7 Hz, 3H); *m/z* = 517 (M+1).

Compound 330: A solution of compound **90** (605 mg, 1.34 mmol) and 2-iodoxybenzoic acid (1.50 g, 5.36 mmol) in DMSO (10 mL) was heated at 65 °C under nitrogen for 26 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, eluting with 50% EtOAc in hexanes) to give compound **330** (437 mg, 73% yield) as a clear glass. *m/z* = 450 (M+1).

Compound 331: To a stirring suspension of potassium hydride (30% dispersion in mineral oil, 280 mg, 2.09 mmol) in anhydrous THF (10 mL) under nitrogen at 0 °C was added dropwise a solution of

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	2
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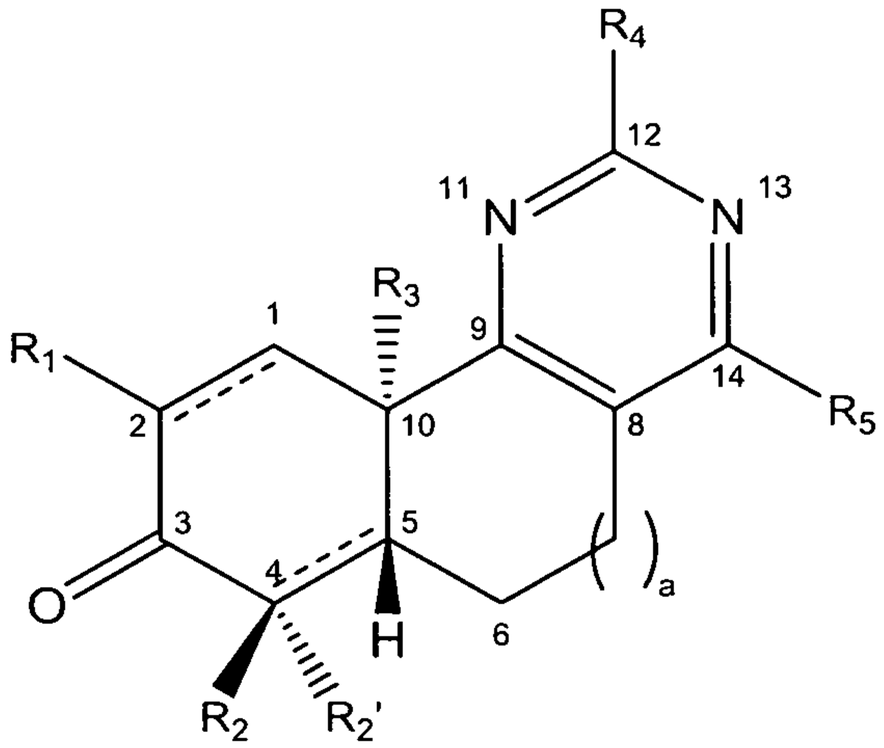
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WHAT IS CLAIMED IS:

1. A compound of the formula:



(I)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of these groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, alkyl$_{(C\leq 18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, amido$_{(C\leq 18)}$, substituted amido$_{(C\leq 18)}$, or

$-X_1-(CH_2)_m-R_4'$;

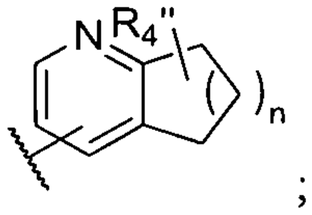
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$-X_2-(CH_2)_p-R_4'''$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$-OY_1-A_1$;

wherein:

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$; or

$-Y_2-C(O)NR_c-A_2$;

wherein:

Y_2 is arenediyl$_{(C\leq 8)}$ or substituted arenediyl$_{(C\leq 8)}$;

R_c is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

A_2 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$; or

$-A_3R_d$;

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

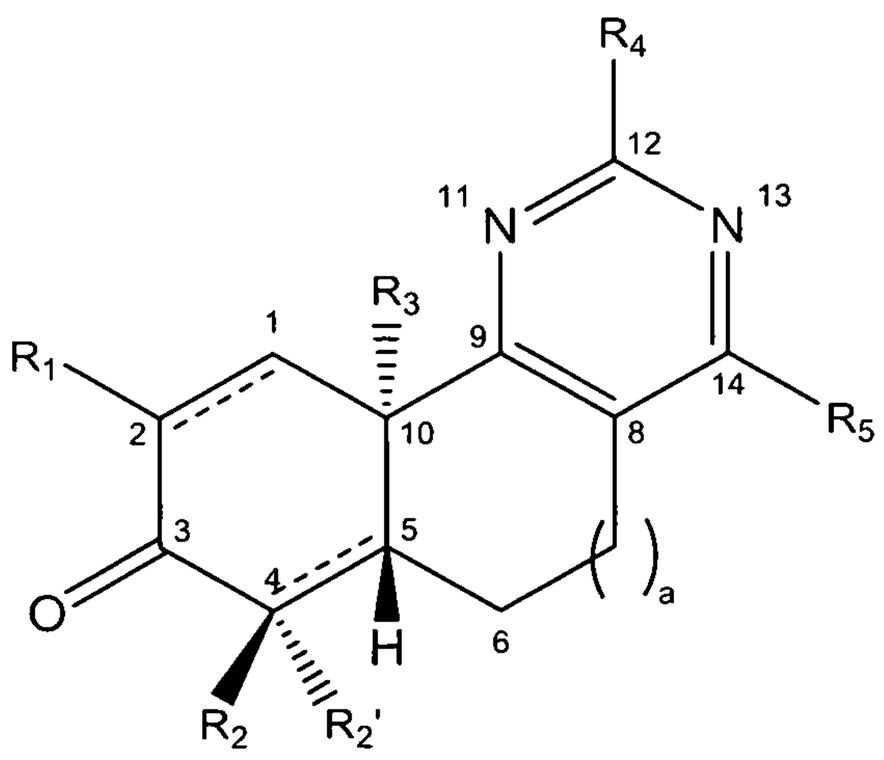
R_e is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

R_d is acyl$_{(C\leq 12)}$, or substituted acyl$_{(C\leq 12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 further defined as:



(I)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of these groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

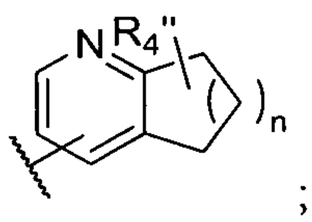
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4''';$$

wherein:

X_2 is arenediyl$_{(C\leq12)}$, substituted arenediyl$_{(C\leq12)}$, heterocycloalkanediyl$_{(C\leq12)}$, substituted heterocycloalkanediyl$_{(C\leq12)}$, heteroarenediyl$_{(C\leq12)}$, or substituted heteroarenediyl$_{(C\leq12)}$;

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

R_4''' is alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, amido$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, $-C(O)-$alkoxy$_{(C\leq8)}$, $-C(O)-$alkylamino$_{(C\leq8)}$, $-C(O)-$dialkyl-amino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, alkyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$; or

$$-Y_2-C(O)NR_c-A_2;$$

wherein:

Y_2 is arenediyl$_{(C\leq8)}$ or substituted arenediyl$_{(C\leq8)}$;

R_c is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

A_2 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$; or

$$-A_3R_d;$$

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

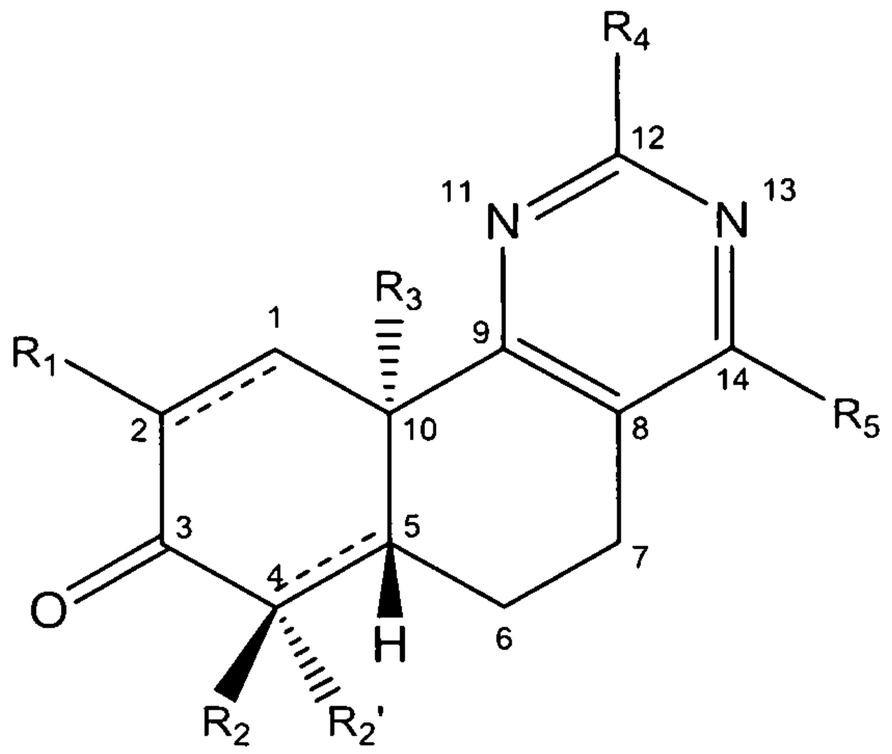
R_e is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

R_d is acyl$_{(C\leq12)}$, or substituted acyl$_{(C\leq12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

3. The compound of either claim 1 or claim 2 further defined as:



(II)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, alkyl$_{(C2\text{-}18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, alkylamino$_{(C\leq 18)}$, substituted alkylamino$_{(C\leq 18)}$, dialkylamino$_{(C\leq 18)}$, substituted dialkylamino$_{(C\leq 18)}$, alkylthio$_{(C\leq 18)}$, substituted alkylthio$_{(C\leq 18)}$, amido$_{(C\leq 18)}$, substituted amido$_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

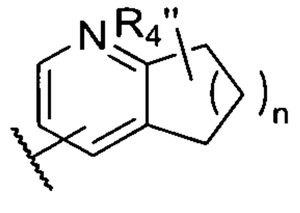
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$-X_2-(CH_2)_p-R_4'''$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C<12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$-OY_1-A_1$;

wherein:

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$; or

$-Y_2-C(O)NR_c-A_2$;

wherein:

Y_2 is arenediyl$_{(C\leq 8)}$ or substituted arenediyl$_{(C\leq 8)}$;

R_c is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

A_2 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$; or

$-A_3R_d$;

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

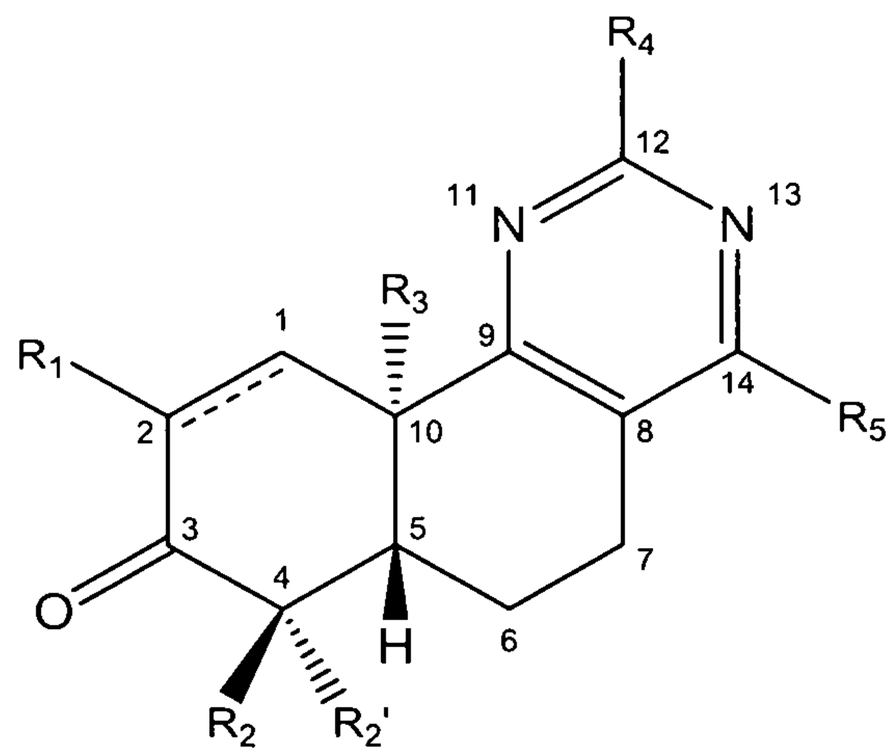
R_e is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

R_d is acyl$_{(C\leq 12)}$, or substituted acyl$_{(C\leq 12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3 further defined as:



(III)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, or a substituted version of the last four groups;

R_3 is $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

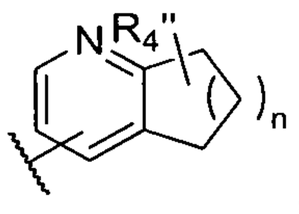
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4''';$$

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2;$$

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d;$$

wherein:

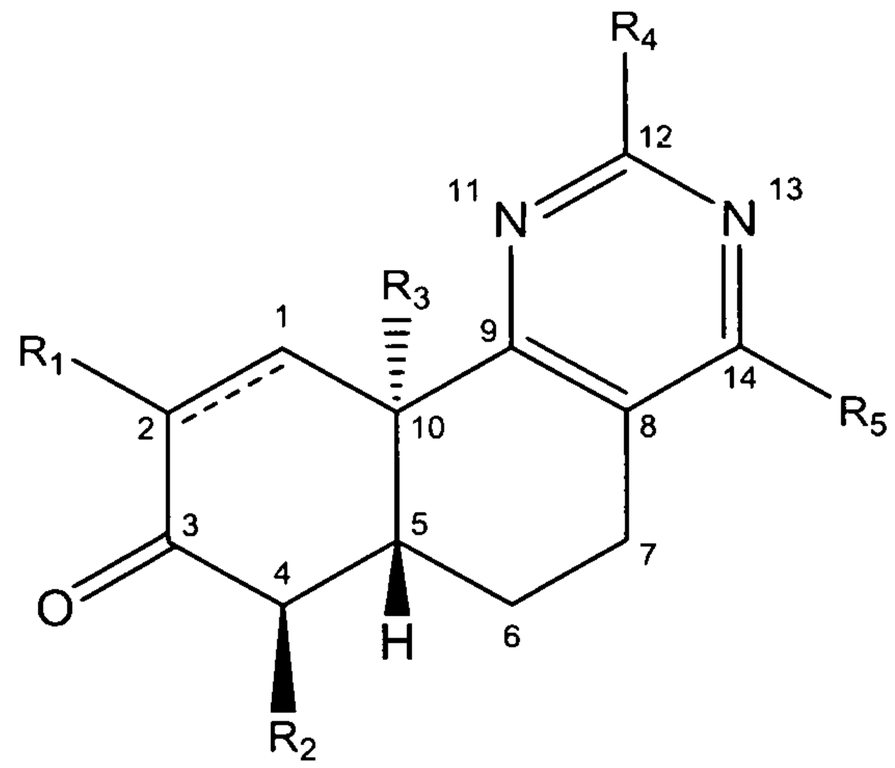
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1-4 further defined as:



(IV)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, heteroaryl$_{(C\leq8)}$, substituted heteroaryl$_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, dialkylamino$_{(C\leq8)}$, alkylsulfonylamino$_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq8)}-$cycloalkyl$_{(C\leq12)}$ or a substituted version of this group;

R_3 is alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, alkyl$_{(C2\text{-}18)}$, substituted alkyl$_{(C\leq18)}$, cycloalkyl$_{(C\leq18)}$, substituted cycloalkyl$_{(C\leq18)}$, aryl$_{(C\leq18)}$, substituted aryl$_{(C\leq18)}$, aralkyl$_{(C\leq18)}$, substituted aralkyl$_{(C\leq18)}$, heteroaryl$_{(C\leq18)}$, substituted heteroaryl$_{(C\leq18)}$, heteroaralkyl$_{(C\leq18)}$, substituted heteroaralkyl$_{(C\leq18)}$, heterocycloalkyl$_{(C\leq18)}$, substituted heterocycloalkyl$_{(C\leq18)}$, alkylamino$_{(C\leq18)}$, substituted alkylamino$_{(C\leq18)}$, dialkylamino$_{(C\leq18)}$, substituted dialkylamino$_{(C\leq18)}$, alkylthio$_{(C\leq18)}$, substituted alkylthio$_{(C\leq18)}$, amido$_{(C\leq18)}$, substituted amido$_{(C\leq18)}$, or

$-X_1-(CH_2)_m-R_4'$;

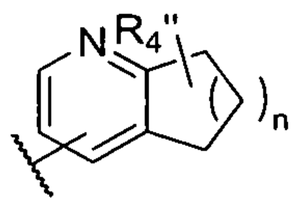
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$;

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

R_4' is alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq18)}$, aryl$_{(C\leq18)}$, aralkyl$_{(C\leq18)}$, heteroaryl$_{(C\leq18)}$, heteroaralkyl$_{(C\leq18)}$, heterocycloalkyl$_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



,

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, amido$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, dialkylamino$_{(C\leq8)}$, $-C(O)-$alkoxy$_{(C\leq8)}$,

$-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq 12)}$, substituted $arenediyl_{(C\leq 12)}$, $heterocycloalkanediyl_{(C\leq 12)}$, substituted $heterocycloalkanediyl_{(C\leq 12)}$, $heteroarenediyl_{(C\leq 12)}$, or substituted $heteroarenediyl_{(C\leq 12)}$;

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

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq 8)}$ or substituted $arenediyl_{(C\leq 8)}$;

R_b is hydrogen, $alkyl_{(C<6)}$, or substituted $alkyl_{(C\leq 6)}$; and

A_2 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$; or

$$-A_3R_d$$;

wherein:

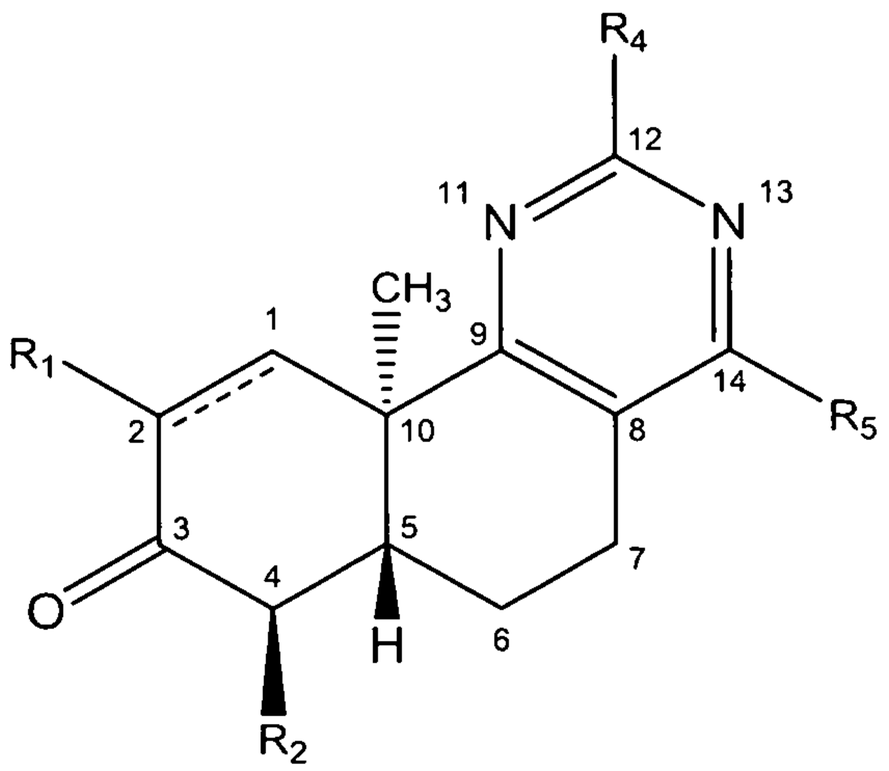
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5 further defined as:



(V)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, alkyl$_{(C2\text{-}18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, alkylamino$_{(C\leq 18)}$, substituted alkylamino$_{(C\leq 18)}$, dialkylamino$_{(C\leq 18)}$, substituted dialkylamino$_{(C\leq 18)}$, alkylthio$_{(C\leq 18)}$, substituted alkylthio$_{(C\leq 18)}$, amido$_{(C\leq 18)}$, substituted amido$_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

wherein:

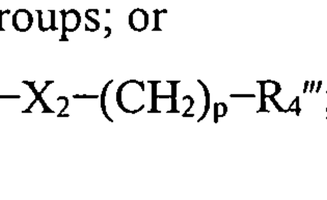
X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

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

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of

any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$-A_3R_d$;

wherein:

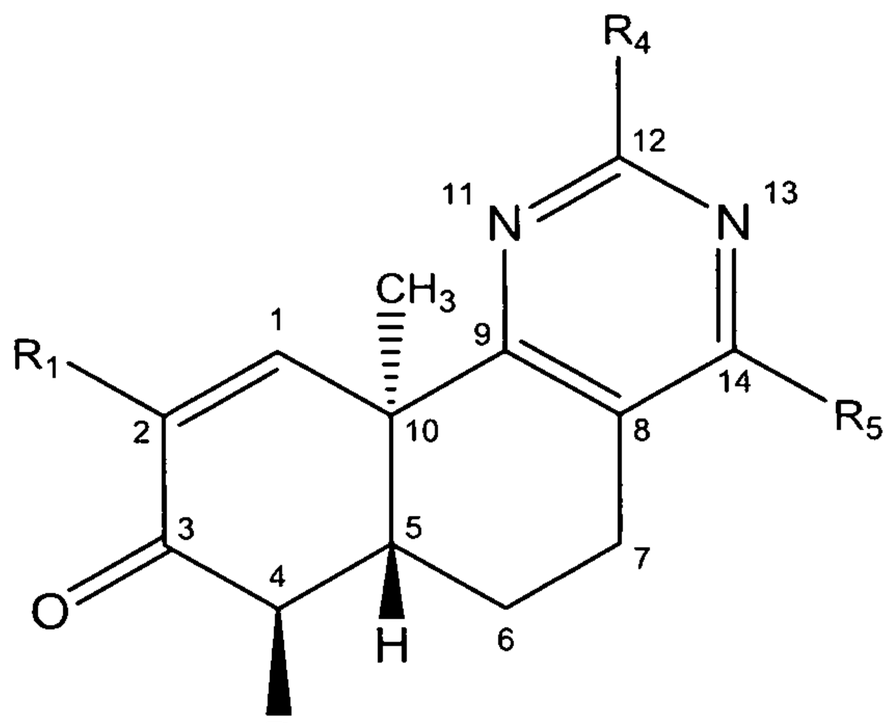
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 6 further defined as:



R_2

(VI)

wherein:

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$-X_1-(CH_2)_m-R_4'$;

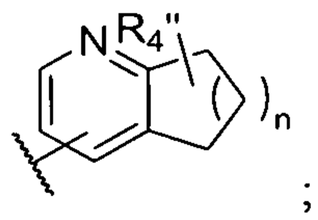
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

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

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; or

$-X_2-(CH_2)_p-R_4'''$;

wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C<12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$-OY_1-A_1$;

wherein:

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$; or

$-Y_2-C(O)NR_b-A_2$;

wherein:

Y_2 is arenediyl$_{(C\leq 8)}$ or substituted arenediyl$_{(C\leq 8)}$;

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

A_2 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$; or

$-A_3R_d$;

wherein:

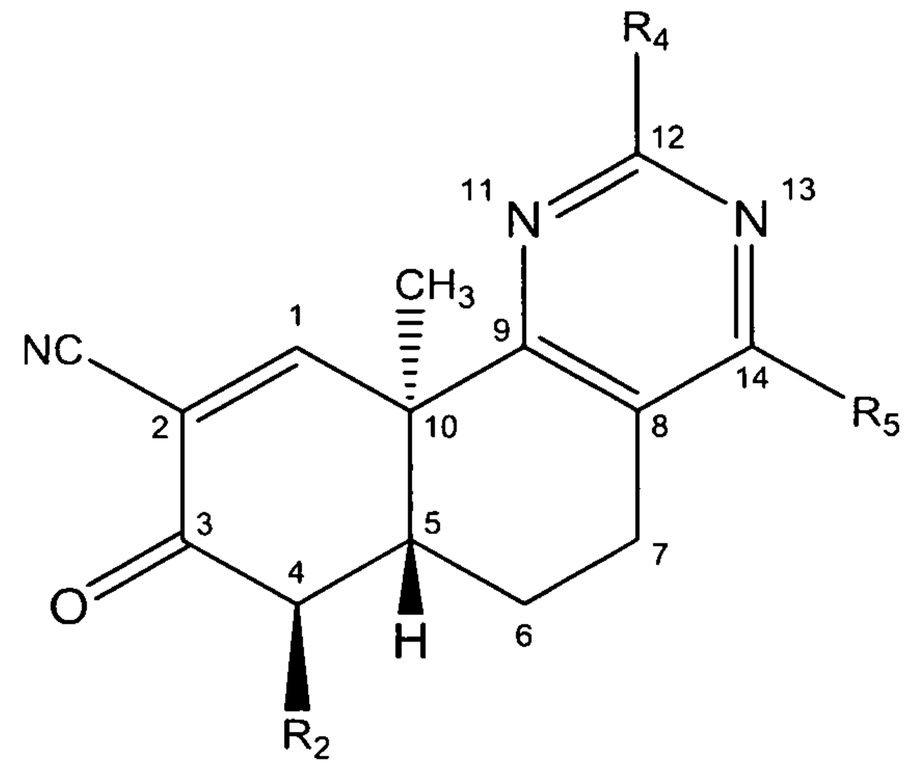
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

R_d is acyl$_{(C\leq 12)}$, or substituted acyl$_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

8. The compound of claim 7 further defined as:



(VII)

wherein:

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, alkyl$_{(C2\text{-}18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, alkylamino$_{(C\leq 18)}$, substituted alkylamino$_{(C\leq 18)}$,

dialkylamino$_{(C\leq18)}$, substituted dialkylamino$_{(C\leq18)}$, alkylthio$_{(C\leq18)}$, substituted alkylthio$_{(C\leq18)}$, amido$_{(C\leq18)}$, substituted amido$_{(C\leq18)}$, or

$-X_1-(CH_2)_m-R_4'$;

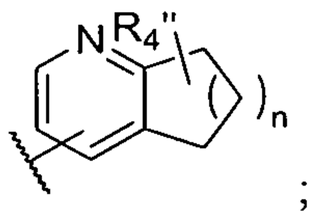
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$;

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

R_4' is alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq18)}$, aryl$_{(C\leq18)}$, aralkyl$_{(C\leq18)}$, heteroaryl$_{(C\leq18)}$, heteroaralkyl$_{(C\leq18)}$, heterocycloalkyl$_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, amido$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, dialkylamino$_{(C\leq8)}$, $-C(O)-$alkoxy$_{(C\leq8)}$, $-C(O)-$alkylamino$_{(C\leq8)}$, $-C(O)-$dialkyl-amino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; or

$-X_2-(CH_2)_p-R_4'''$;

wherein:

X_2 is arenediyl$_{(C\leq12)}$, substituted arenediyl$_{(C\leq12)}$, heterocycloalkanediyl$_{(C\leq12)}$, substituted heterocycloalkanediyl$_{(C\leq12)}$, heteroarenediyl$_{(C\leq12)}$, or substituted heteroarenediyl$_{(C\leq12)}$;

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

R_4''' is alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, amido$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, $-C(O)-$alkoxy$_{(C\leq8)}$, $-C(O)-$alkylamino$_{(C\leq8)}$, $-C(O)-$dialkyl-amino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, alkyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$,

dialkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$; or

$$-Y_2-C(O)NR_b-A_2;$$

wherein:

Y_2 is arenediyl$_{(C\leq8)}$ or substituted arenediyl$_{(C\leq8)}$;

R_b is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

A_2 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$; or

$$-A_3R_d;$$

wherein:

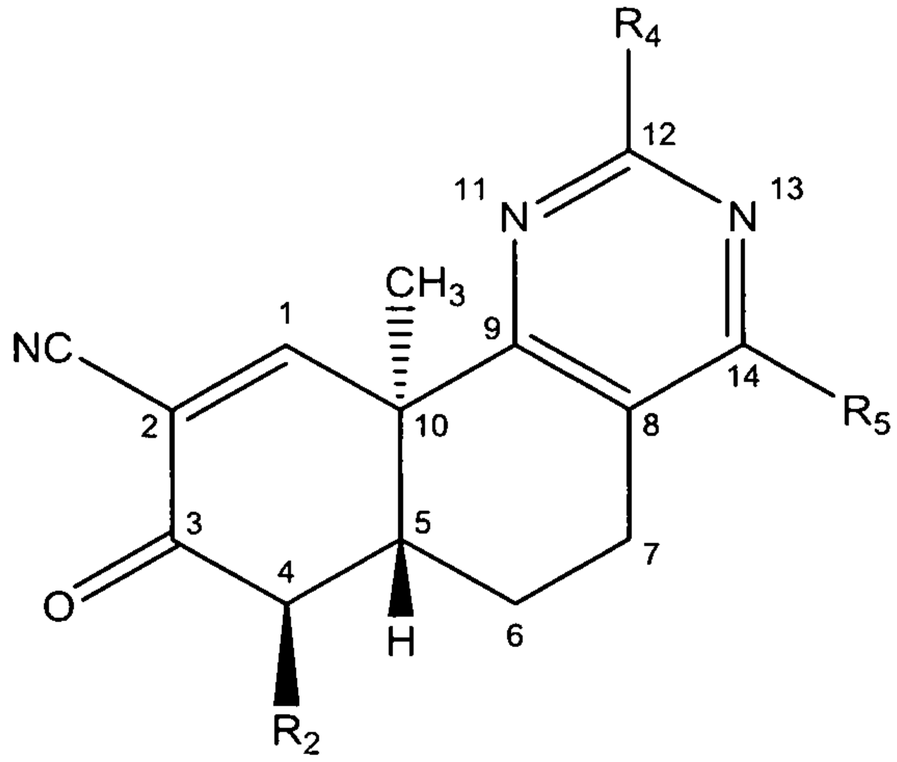
A_3 is $-O-$ or $-NR_e-$, wherein

R_e is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

R_d is acyl$_{(C\leq12)}$, or substituted acyl$_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 8 further defined as:



(VII)

wherein:

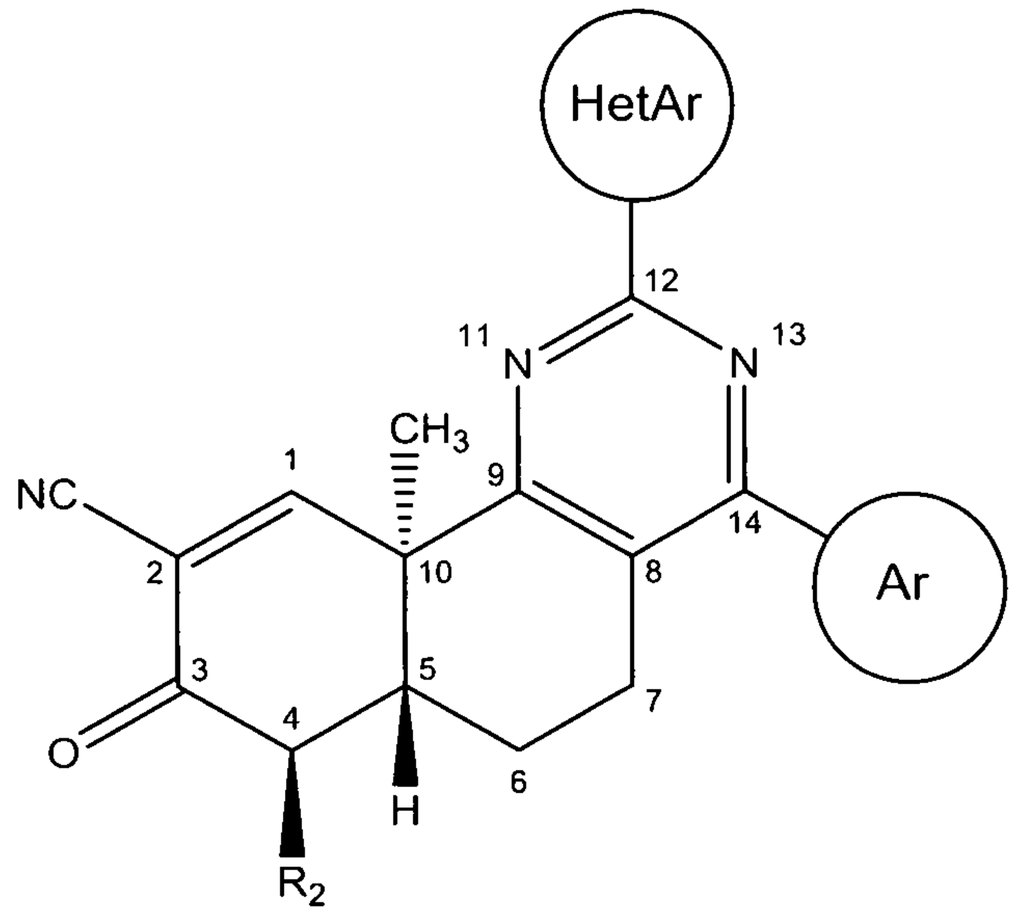
R_2 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$;

R_4 is heteroaryl$_{(C\leq18)}$ or substituted heteroaryl$_{(C\leq18)}$; and

R_5 is aryl$_{(C\leq12)}$ or substituted aryl$_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 8 further defined as:



(VIII)

wherein:

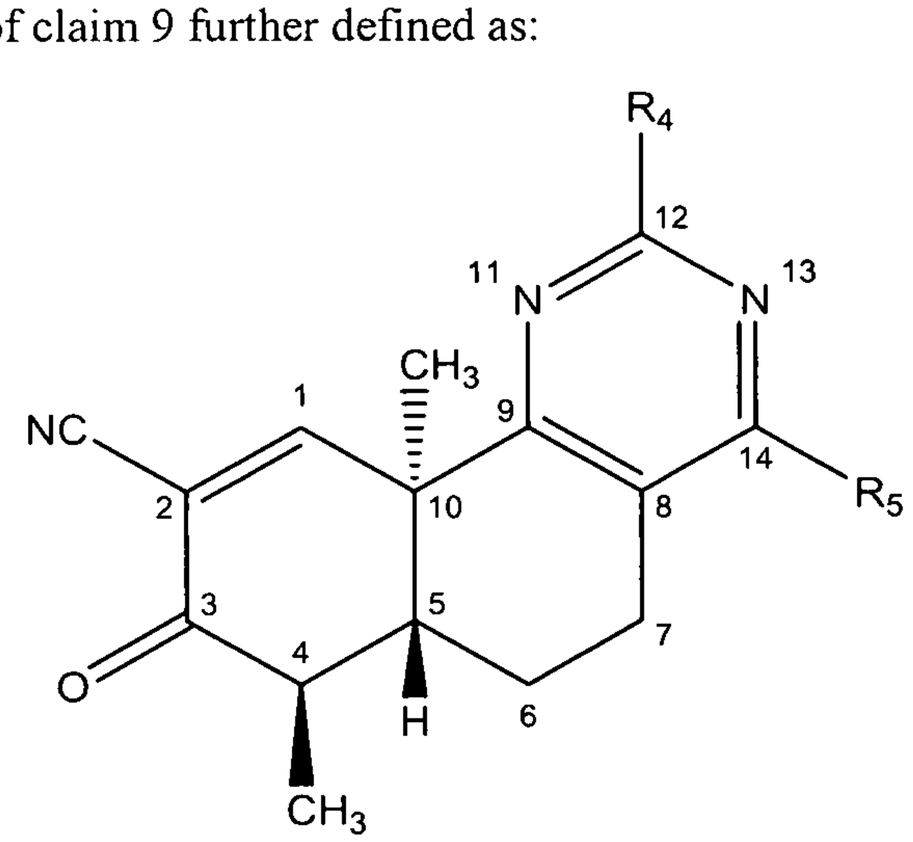
R_2 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$;

HetAr is $heteroaryl_{(C\leq18)}$ or substituted $heteroaryl_{(C\leq18)}$; and

Ar is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 9 further defined as:



(IX)

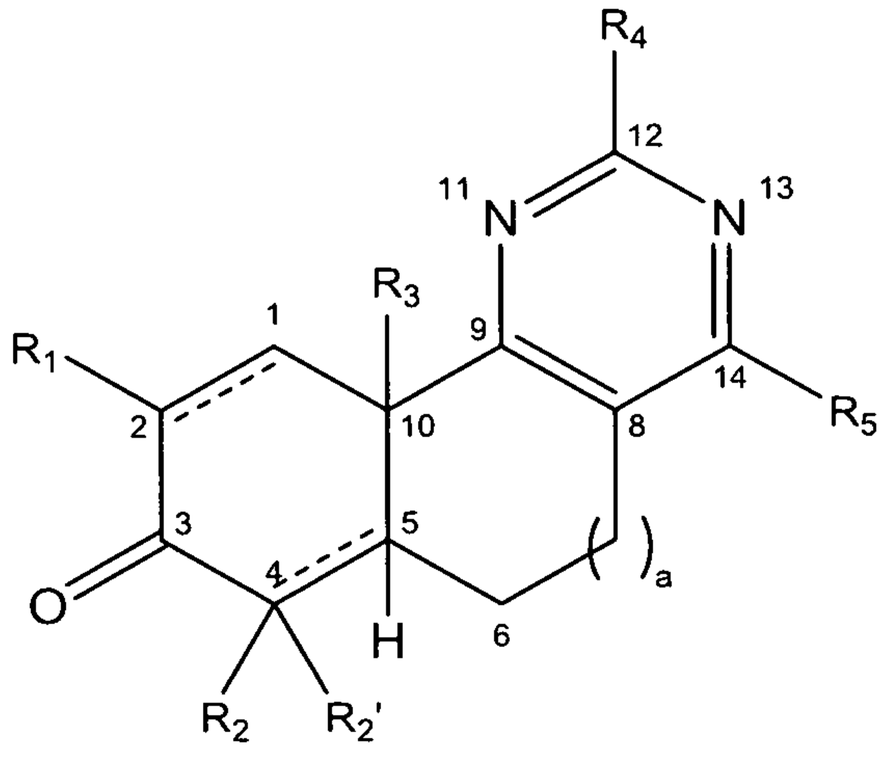
wherein:

R_4 is $heteroaryl_{(C\leq18)}$ or substituted $heteroaryl_{(C\leq18)}$; and

R_5 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

12. A compound of the formula:



(X)

wherein:

the bond between carbon atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, or $-X_1-(CH_2)_m-R_4'$;

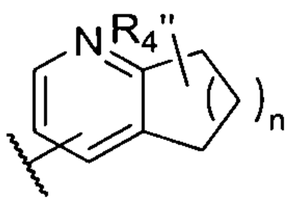
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

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

R_4' is $cycloalkyl_{(C\leq 18)}$, $aryl_{(C\leq 18)}$, $aralkyl_{(C\leq 18)}$, $heteroaryl_{(C\leq 18)}$, $heteroaralkyl_{(C\leq 18)}$, $heterocycloalkyl_{(C\leq 18)}$, or a substituted version of any of these groups; or



;

wherein:

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

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq 12)}$, substituted $arenediyl_{(C\leq 12)}$, $heterocycloalkyldiyl_{(C\leq 12)}$, substituted $heterocycloalkyldiyl_{(C\leq 12)}$, $heteroarenediyl_{(C\leq 12)}$, or substituted $heteroarenediyl_{(C\leq 12)}$;

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

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, or a substituted version of any of the last three groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

13. The compound according to any one of claims 1-6 and 12, wherein the bond between carbon atom 1 and carbon atom 2 is an epoxidized double bond.

14. The compound according to any one of claims 1-6 and 12, wherein the bond between carbon atom 1 and carbon atom 2 is a double bond.

15. The compound according to any one of claims 1-3 and 12-14, wherein the bond between carbon atom 4 and carbon atom 5 is a single bond.

16. The compound according to any one of claims 1-3 and 12-14, wherein the bond between carbon atom 4 and carbon atom 5 is a double bond.

17. The compound according to any one of claims 1, 2, and 12-16, wherein a is 1.

18. The compound according to any one of claims 1, 2, and 12-16, wherein a is 0.

19. The compound according to any one of claims 1, 2, and 12-16, wherein a is 2.

20. The compound according to any one of claims 1-7 and 12-19, wherein R_1 is cyano.

21. The compound according to any one of claims 1-10 and 12-20, wherein R_2 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$.

22. The compound of claim 21, wherein R_2 is $alkyl_{(C\leq12)}$.

23. The compound of claim 22, wherein R_2 is methyl, ethyl, or propyl.

24. The compound of claim 23, wherein R_2 is methyl.

25. The compound of claim 21, wherein R_2 is substituted $alkyl_{(C\leq12)}$.

26. The compound of claim 25, wherein R_2 is 3-hydroxypropyl.

27. The compound according to any one of claims 1-10 and 12-20, wherein R_2 is $alkenyl_{(C\leq12)}$ or substituted $alkenyl_{(C\leq12)}$.

28. The compound of claim 27, wherein R_2 is $alkenyl_{(C\leq12)}$.

29. The compound of claim 28, wherein R_2 is 2-propenyl or 2-methyl-prop-2-enyl.

30. The compound according to any one of claims 1-4 and 12-29, wherein R_2' is hydrogen.

31. The compound according to any one of claims 1-4 and 12-29, wherein R_2' is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$.

32. The compound of claim 31, wherein R_2' is $alkyl_{(C\leq12)}$.

33. The compound of claim 32, wherein R_2' is methyl.

34. The compound according to any one of claims 1-5 and 12-33, wherein R_3 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$.

35. The compound of claim 34, wherein R_3 is $alkyl_{(C\leq12)}$.

36. The compound of claim 35, wherein R_3 is methyl, propyl, or isopentyl.

37. The compound of claim 36, wherein R_3 is methyl.

38. The compound according to any one of claims 1-5 and 12-33, wherein R_3 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$.

39. The compound of claim 38, wherein R_3 is $aryl_{(C\leq12)}$.

40. The compound of claim 39, wherein R_3 is phenyl.

41. The compound according to any one of claims 1-8 and 13-40, wherein R_4 is $alkyl_{(C2-18)}$ or substituted $alkyl_{(C2-18)}$.

42. The compound according to any one of claims 1-40, wherein R_4 is $heteroaryl_{(C\leq18)}$ or substituted $heteroaryl_{(C\leq18)}$.

43. The compound of claim 42, wherein R_4 is a $heteroaryl_{(C\leq12)}$ or a substituted $heteroaryl_{(C\leq12)}$ group wherein at least one of the heteroatoms in the aromatic ring is a nitrogen atom.

44. The compound of claim 42, wherein R_4 is $heteroaryl_{(C\leq18)}$.

45. The compound of claim 44, wherein R_4 is 3-pyridinyl, 4-pyridinyl, 4-(2-cycylopropyl)-pyridinyl, 5-(2-cycylopropyl)-pyridinyl, 4-(2-morpholino)-pyridinyl, 4-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 3-(6-methyl)-pyridinyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-pyrazolo[1,5-*a*]pyridinyl, 3-(*N*-methyl)-pyrrolo[2,3-*b*]pyridinyl, 5-isoquinlinyl, 2-isoquinlinyl, 1-isoquinolinyl, 4-(2-phenyl)-pyridinyl, 5-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 4-(3,5-dimethyl)-isoxazolyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-(4-methyl)-pyridinyl, 4-(6-methyl)-pyrimidinyl, 6-(4-methyl)-pyrimidinyl, 4-pyridazinyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 5-quinolinyl, 6-quinolinyl, 8-quinolinyl, 4-isoquinolinyl, 3-(8-methyl)-quinolinyl, 3-(1-methyl)-quinolinyl, 4-(2-methyl)-quinolinyl, 4-(2-isopropyl)-quinolinyl, 4-(6-methyl)-quinolinyl, 4-(7-methyl)-quinolinyl, 4-(8-methyl)-quinolinyl, 2-(*N*-methyl)-indolyl, 5-(2,4-dimethyl)-thiazolyl, or 5-(3-methyl)-oxadizolyl.

46. The compound of claim 42, wherein R_4 is substituted $heteroaryl_{(C\leq18)}$.

47. The compound of claim 46, wherein R_4 is 4-(2-trifluoromethyl)-pyridinyl, 4-(3-fluoro)-pyridinyl, 4-(2-methoxy)-pyridinyl, 4-(2-hydroxymethyl)-pyridinyl, 4-(2-acetylamino)-pyridinyl, 4-(2-fluoromethyl)-pyridinyl, 4-(2-acetamidylethyl)-pyridinyl, 4-(2-fluoromethyl)-quinolinyl, 4-(2-acetoxymethyl)-quinolinyl, 4-(2-formyl)-quinolinyl, 4-(6-fluoro)-quinolinyl, 4-(7-fluoro)-quinolinyl, 4-(8-fluoro)-quinolinyl, 4-(6,8-difluoro)-quinolinyl, 4-(6-fluoro-2-methyl)-quinolinyl, or 4-(8-fluoro-2-methyl)-quinolinyl.

48. The compound according to any one of claims 1-8 and 13-40, wherein R_4 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$.

49. The compound of claim 48, wherein R_4 is $aryl_{(C\leq12)}$.

50. The compound of claim 49, wherein R_4 is phenyl.

51. The compound of claim 48, wherein R_4 is substituted $aryl_{(C\leq12)}$.

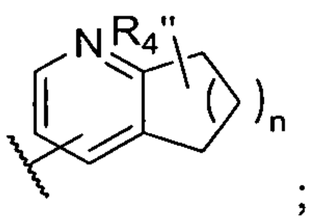
52. The compound of claim 51, wherein R_4 is 2-fluorophenyl or 4-trifluoromethylphenyl.

53. The compound according to any one of claims 1-8 and 12-40, wherein R_4 is $cycloalkyl_{(C\leq12)}$ or substituted $cycloalkyl_{(C\leq12)}$.

54. The compound of claim 53, wherein R_4 is $cycloalkyl_{(C\leq12)}$.

55. The compound of claim 54, wherein R_4 is cyclohexyl.

56. The compound according to any one of claims 1-8 and 12-40, wherein R_4 is:



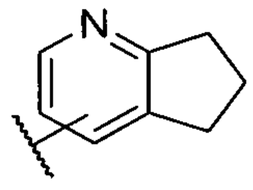
;

wherein:

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

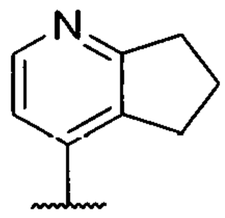
R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups.

57. The compound of claim 56, wherein R_4 is:



.

58. The compound of claim 56, wherein R_4 is:



.

59. The compound according to any one of claims 1-8 and 12-40, wherein R_4 is $heterocycloalkyl_{(C\leq18)}$ or substituted $heterocycloalkyl_{(C\leq18)}$.

60. The compound of claim 59, wherein R_4 is heterocycloalkyl$_{(C\leq12)}$.

61. The compound of claim 60, wherein R_4 is morpholinyl, 4-piperidinyl, 3-(5-methyl-)1,2,3,6-tetrahydropyridinyl, or 4-*N*-methylpiperazinyl.

62. The compound of claim 59, wherein R_4 is substituted heterocycloalkyl$_{(C\leq12)}$.

63. The compound of claim 62, wherein R_4 is *N*-*t*-butyloxycarbonyl-4-piperidinyl, *N*-acetyl-4-piperidinyl, *N*-*t*-butyloxycarbonyl-5-methyl-1,2,3,6-tetrahydropyridinyl, *N*-acetyl-5-methyl-1,2,3,6-tetrahydropyridinyl, or 4-*N*-acetylpiperazinyl.

64. The compound according to any one of claims 1-8 and 13-40, wherein R_4 is hydrogen.

65. The compound according to any one of claims 1-8 and 12-40, wherein R_4 is $-X_1-(CH_2)_m-R_4'$; wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$;

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

R_4' is alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq18)}$, aryl$_{(C\leq18)}$, aralkyl$_{(C\leq18)}$, heteroaryl$_{(C\leq18)}$, heteroaralkyl$_{(C\leq18)}$, heterocycloalkyl$_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl.

66. The compound of claim 65, wherein X_1 is NR_b, wherein: R_b is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$.

67. The compound of either claim 65 or claim 66, wherein R_b is hydrogen.

68. The compound according to any one of claims 65-67, wherein m is 0 or 1.

69. The compound of claim 68, wherein m is 0.

70. The compound according to any one of claims 65-69, wherein R_4' is cycloalkyl$_{(C\leq18)}$, aryl$_{(C\leq18)}$, aralkyl$_{(C\leq18)}$, heteroaryl$_{(C\leq18)}$, heteroaralkyl$_{(C\leq18)}$, heterocycloalkyl$_{(C\leq18)}$, or a substituted version of any of these groups.

71. The compound according to any one of claims 65-70, wherein R_4' is heteroaryl$_{(C\leq12)}$ or substituted heteroaryl$_{(C\leq12)}$.

72. The compound of claim 71, wherein R_4' is heteroaryl$_{(C\leq12)}$.

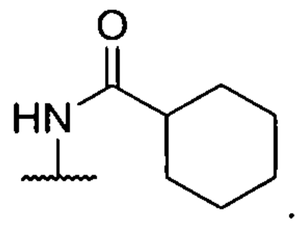
73. The compound of claim 72, wherein R_4' is 4-pyridinyl.

74. The compound according to any one of claims 1-8 and 13-40, wherein R_4 is amino.

75. The compound according to any one of claims 1-8 and 13-40, wherein R_4 is amido$_{(C\leq12)}$ or substituted amido$_{(C\leq12)}$.

76. The compound of claim 75, wherein R_4 is amido$_{(C\leq12)}$.

77. The compound of claim 76, wherein R_4 is:



78. The compound according to any one of claims 1-8 and 12-40, wherein R_4 is $-X_2-(CH_2)_p-R_4'''$; wherein:

X_2 is $arenediyl_{(C\leq12)}$, substituted $arenediyl_{(C\leq12)}$, $heterocycloalkanediyl_{(C\leq12)}$, substituted $heterocycloalkanediyl_{(C\leq12)}$, $heteroarenediyl_{(C\leq12)}$, or substituted $heteroarenediyl_{(C\leq12)}$;

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

R_4''' is $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkylamino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups.

79. The compound of claim 78, wherein X_2 is $heteroarenediyl_{(C\leq12)}$ or substituted $heteroarenediyl_{(C\leq12)}$.

80. The compound of claim 79, wherein X_2 is $heteroarenediyl_{(C\leq12)}$.

81. The compound of claim 80, wherein X_2 is pyridin-2,4-diyl or pyridine-2,5-diyl.

82. The compound of claim 78, wherein X_2 is $heterocycloalkanediyl_{(C\leq12)}$ or substituted $heterocycloalkanediyl_{(C\leq12)}$.

83. The compound of claim 82, wherein X_2 is $heterocycloalkanediyl_{(C\leq12)}$.

84. The compound of claim 83, wherein X_2 is piperidin-1,4-diyl, piperazin-1,4-diyl, or 1,2,3,6-tetrahydropiperidin-1,5-diyl.

85. The compound according to any one of claims 78-84, wherein p is 0, 1, or 2.

86. The compound of claim 85, wherein p is 0.

87. The compound of claim 85, wherein p is 1.

88. The compound of claim 85, wherein p is 2.

89. The compound according to any one of claims 78-88, wherein R_4''' is $acyl_{(C\leq8)}$ or substituted $acyl_{(C\leq8)}$.

90. The compound of claim 89, wherein R_4''' is $acyl_{(C\leq8)}$.

91. The compound of claim 90, wherein R_4''' is acetyl.

92. The compound of claim 89, wherein R_4''' is substituted $acyl_{(C\leq8)}$.

93. The compound of claim 92, wherein R_4''' is carboxy.

94. The compound according to any one of claims 78-88, wherein R_4''' is $amido_{(C\leq8)}$ or substituted $amido_{(C\leq8)}$.

95. The compound of claim 94, wherein R_4''' is $amido_{(C\leq8)}$.

96. The compound of claim 95, wherein R_4''' is acetamidyl.

97. The compound according to any one of claims 78-88, wherein R_4''' is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$.

98. The compound of claim 97, wherein R_4''' is $cycloalkyl_{(C\leq8)}$.

99. The compound of claim 98, wherein R_4''' is cyclopropyl.

100. The compound according to any one of claims 78-88, wherein R_4''' is $alkylsulfonyl_{(C\leq8)}$ or substituted $alkylsulfonyl_{(C\leq8)}$.

101. The compound of claim 100, wherein R_4''' is $alkylsulfonyl_{(C\leq8)}$.

102. The compound of claim 101, wherein R_4''' is $-S(O)_2CH_3$ or $-S(O)_2CH_2CH_3$.

103. The compound according to any one of claims 78-88, wherein R_4''' is $-C(O)-alkoxy_{(C\leq8)}$.

104. The compound of claim 103, wherein R_4''' is $-C(O)OEt$.

105. The compound according to any one of claims 78-88, wherein R_4''' is $-C(O)-dialkylamino_{(C\leq8)}$.

106. The compound of claim 105, wherein R_4''' is $-C(O)NMe_2$.

107. The compound according to any one of claims 1-77, wherein R_5 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$.

108. The compound of claim 107, wherein R_5 is $aryl_{(C\leq12)}$.

109. The compound of claim 108, wherein R_5 is phenyl, 4-methylphenyl, 3-isopropylphenyl, 4-isopropylphenyl, 1,3-biphenyl, or 1,4-biphenyl.

110. The compound of claim 107, wherein R_5 further comprises one or more fluorine atoms.

111. The compound of either claim 107 or claim 110, wherein R_5 is substituted $aryl_{(C\leq12)}$.

112. The compound of claim 111, wherein R_5 is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 4-hydroxymethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, or 3,4-dichlorophenyl.

113. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is $cycloalkyl_{(C\leq12)}$ or substituted $cycloalkyl_{(C\leq12)}$.

114. The compound of claim 113, wherein R_5 is cyclopropyl.

115. The compound according to any one of claims 1-8 and 12-77, wherein R_5 is $cycloalkoxy_{(C\leq12)}$ or substituted $cycloalkoxy_{(C\leq12)}$.

116. The compound of claim 113, wherein R_5 is cyclobutyloxy, cyclopentyloxy, or cyclohexyloxy.

117. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of either of these groups.

118. The compound of claim 117, wherein R_5 is $dialkylamino_{(C\leq12)}$ or substituted $dialkylamino_{(C\leq12)}$.

119. The compound of claim 118, wherein R_5 is $dialkylamino_{(C\leq8)}$ or substituted $dialkylamino_{(C\leq8)}$.

120. The compound of claim 119, wherein R_5 is dimethylamino.

121. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is $alkylsulfonylamino_{(C\leq12)}$ or substituted $alkylsulfonylamino_{(C\leq12)}$.

122. The compound of claim 121, wherein R_6 is methylsulfonylamino.

123. The compound according to any one of claims 1-8 and 12-77, wherein R_5 is $-OY_1-A$; wherein:

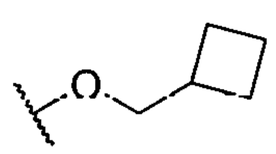
Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$.

124. The compound of claim 123, wherein Y_1 is methylene.

125. The compound of either claim 123 or claim 124, wherein A_1 is cyclobutyl.

126. The compound of claim 123, wherein R_5 is:



.

127. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is $-Y_2-C(O)NR_c-A_2$; wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_c is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$.

128. The compound of claim 127, wherein Y_2 is arenediyl$_{(C\leq 8)}$.

129. The compound of claim 128, wherein Y_2 is benzenediyl.

130. The compound according to any one of claims 127-129, wherein R_c is alkyl$_{(C\leq 6)}$.

131. The compound of claim 130, wherein R_c is methyl.

132. The compound according to any one of claims 127-131, wherein A_2 is aralkyl$_{(C\leq 12)}$.

133. The compound of claim 132, wherein A_2 is benzyl.

134. The compound according to any one of claims 1-8 and 12-77, wherein R_5 is heteroaryl$_{(C\leq 12)}$ or substituted heteroaryl$_{(C\leq 12)}$.

135. The compound of claim 134, wherein R_5 is heteroaryl$_{(C\leq 12)}$.

136. The compound of claim 135, wherein R_5 is 5-(3-methyl)-oxadiazolyl, 4-(3,5-dimethyl)-isoxazolyl, furanyl, benzofuranyl, 2-thiazolyl, 5-(2-methyl)-furanyl, 3-pyridinyl, or 4-pyridinyl.

137. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is hydroxy.

138. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is $-OS(O)_2C_6H_4CH_3$.

139. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is heterocycloalkyl$_{(C\leq 12)}$ or substituted heterocycloalkyl$_{(C\leq 12)}$.

140. The compound of claim 139, wherein R_5 is heterocycloalkyl$_{(C\leq 12)}$.

141. The compound of claim 140, wherein R_5 is pyrrolidinyl.

142. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is alkoxy$_{(C\leq 12)}$ or substituted alkoxy$_{(C\leq 12)}$.

143. The compound of claim 142, wherein R_5 is alkoxy$_{(C\leq 12)}$.

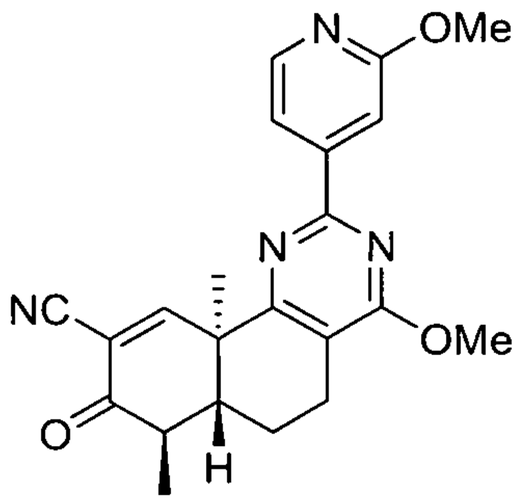
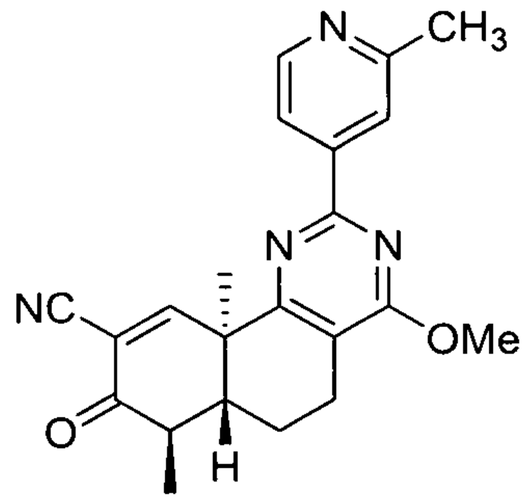
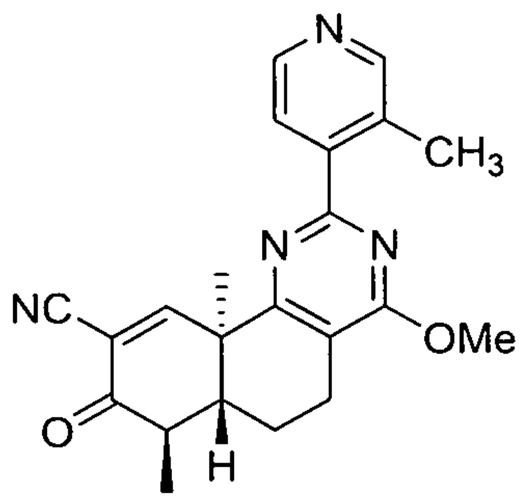
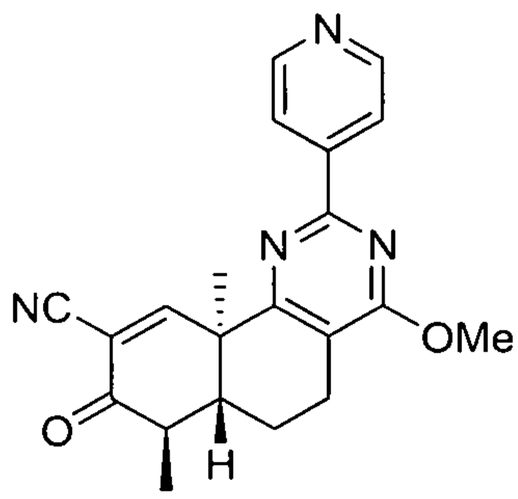
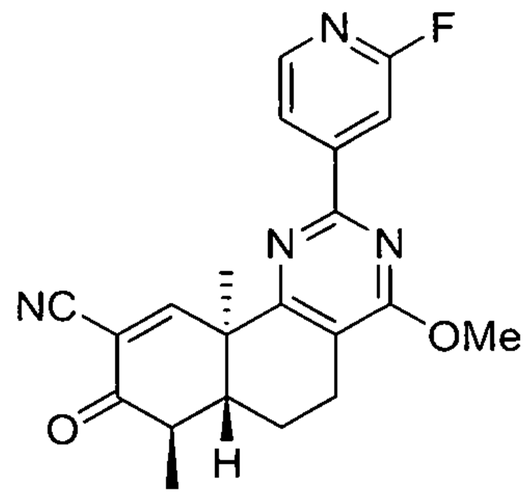
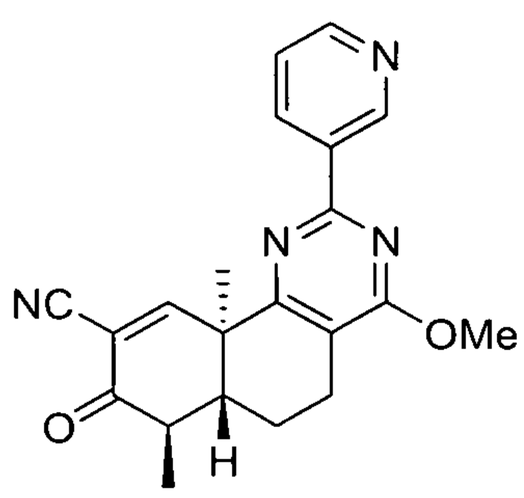
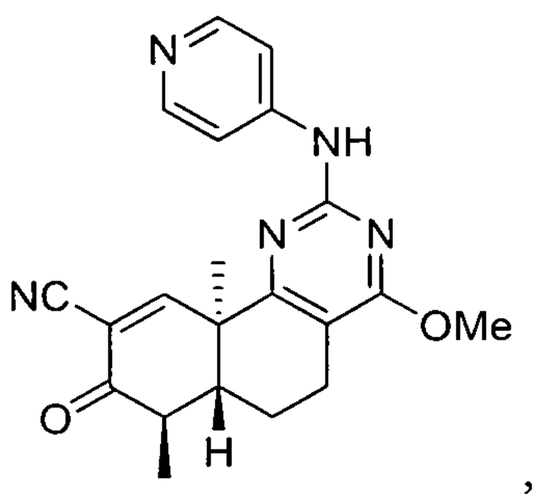
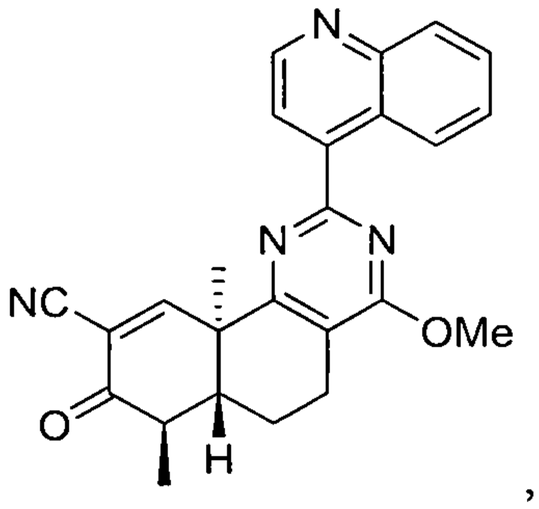
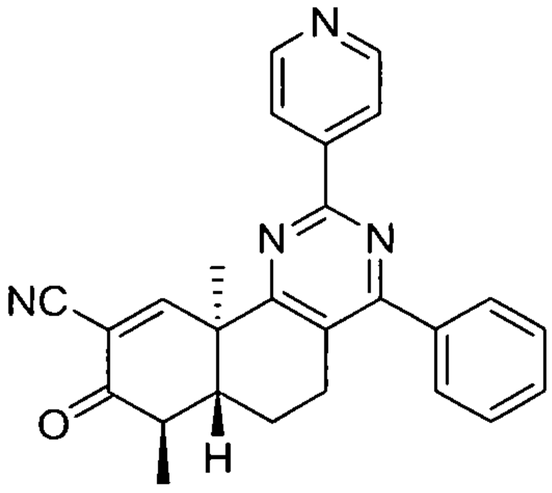
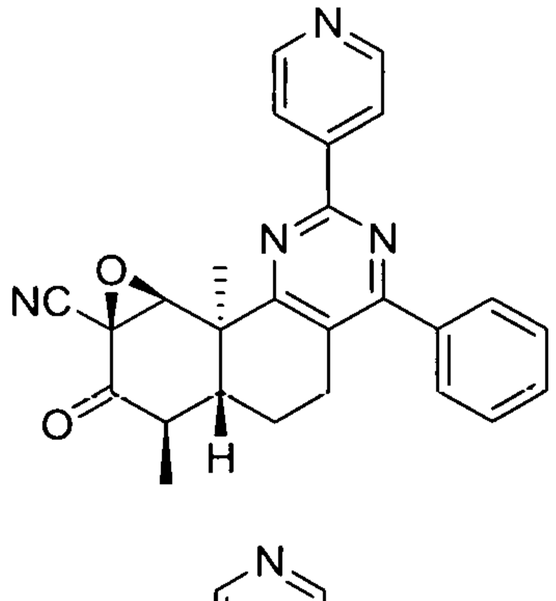
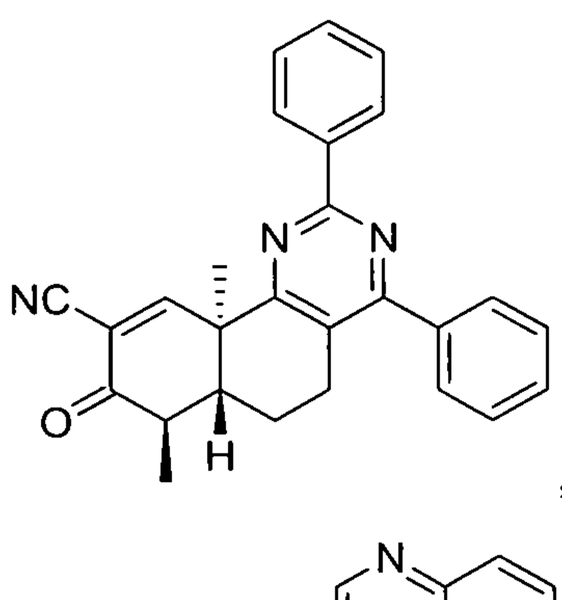
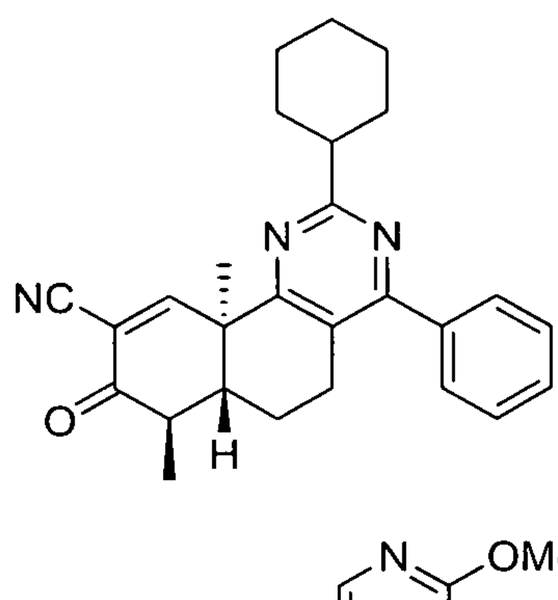
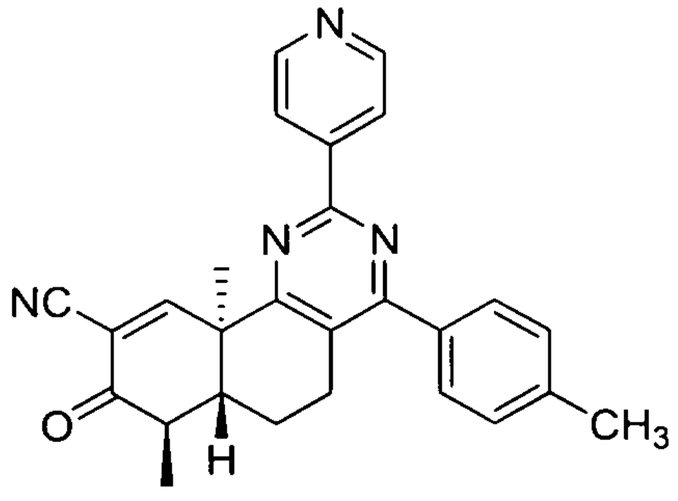
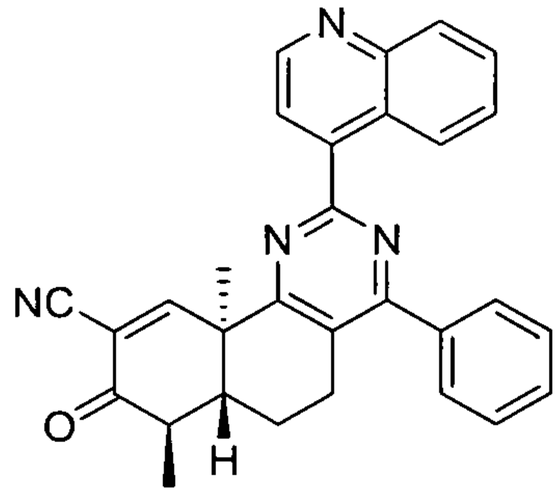
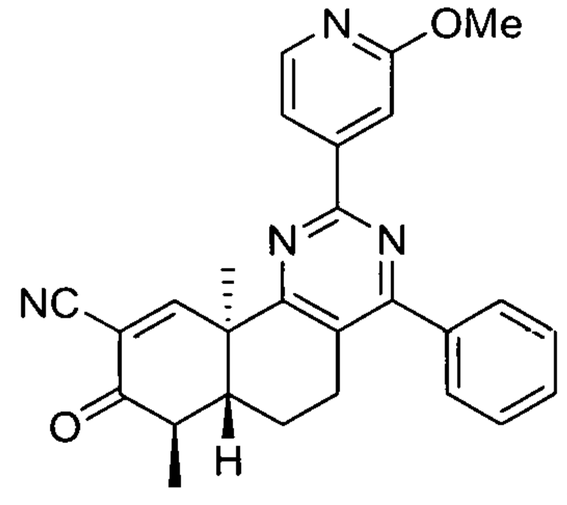
144. The compound of claim 143, wherein R_5 is methoxy or isopropoxy.

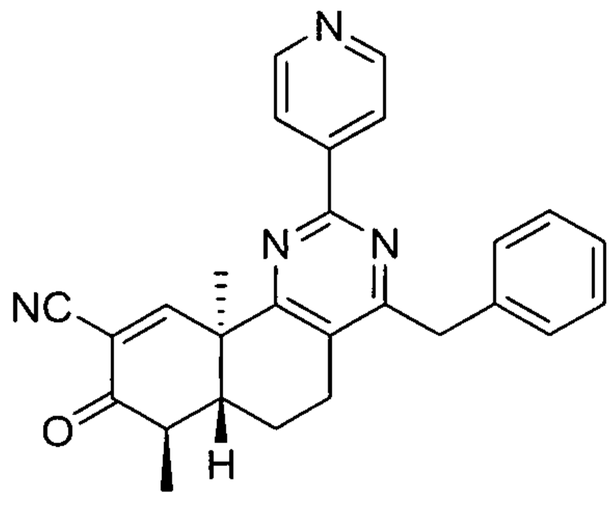
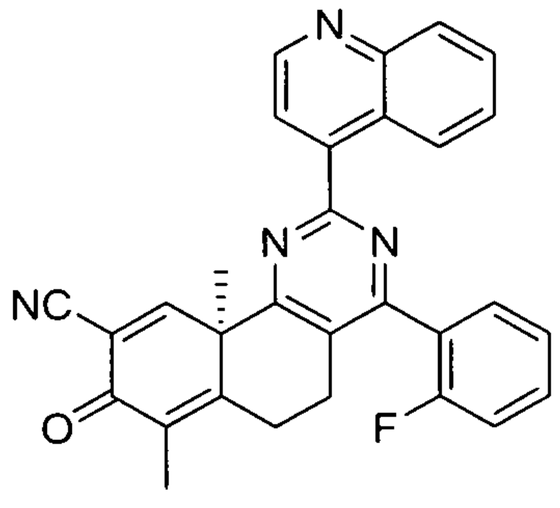
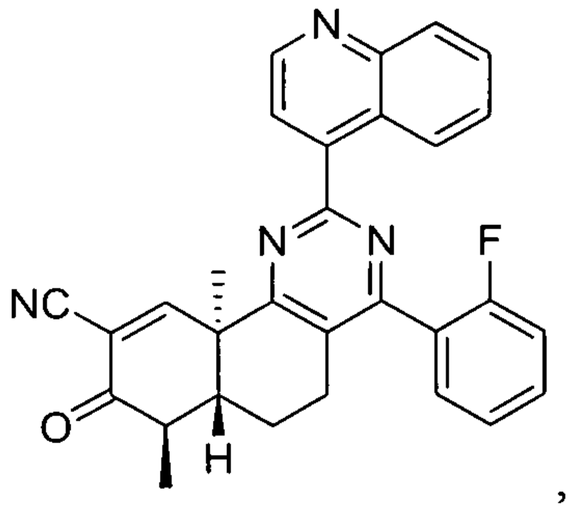
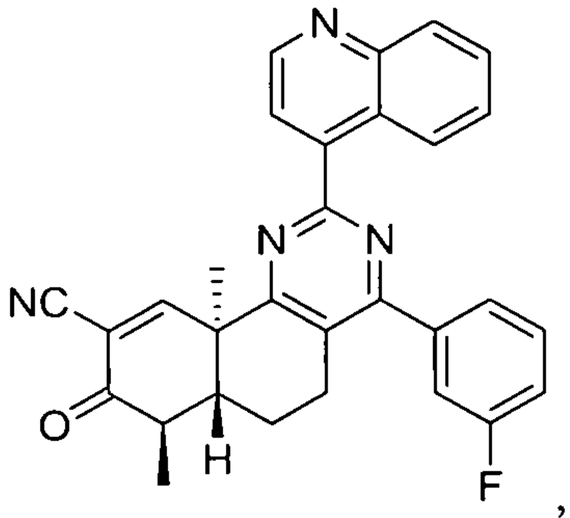
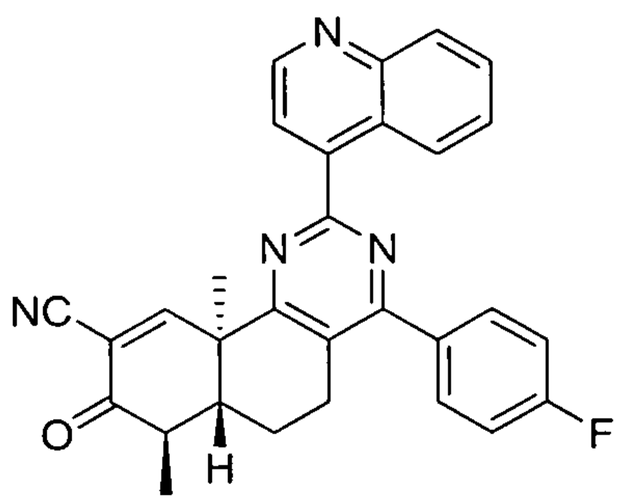
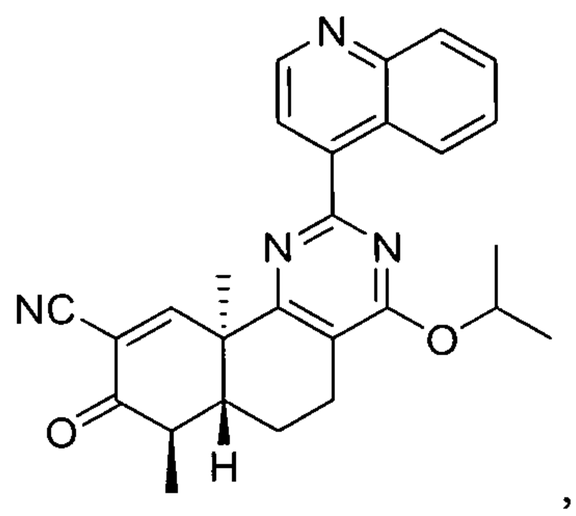
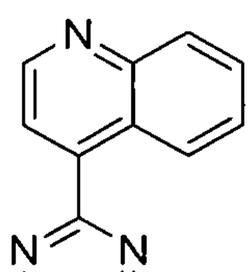
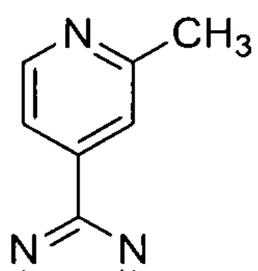
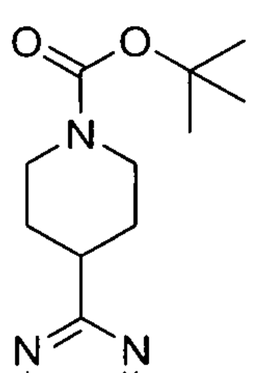
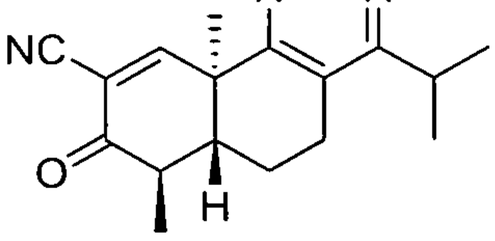
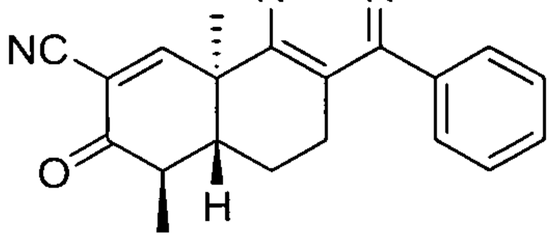
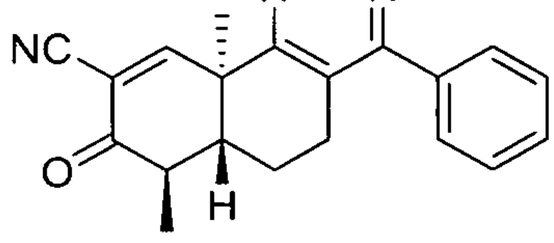
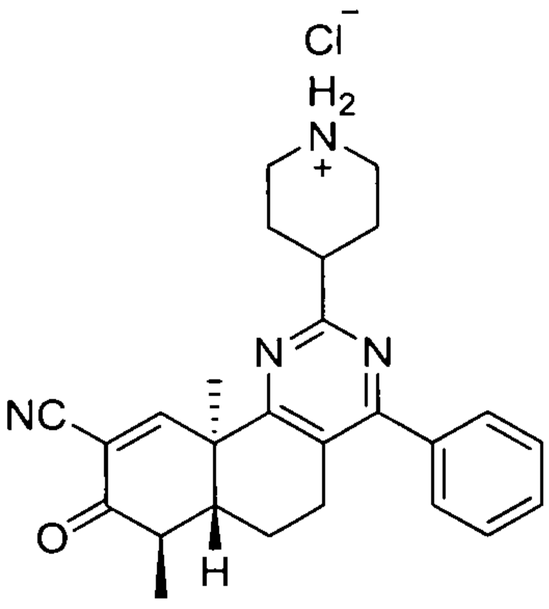
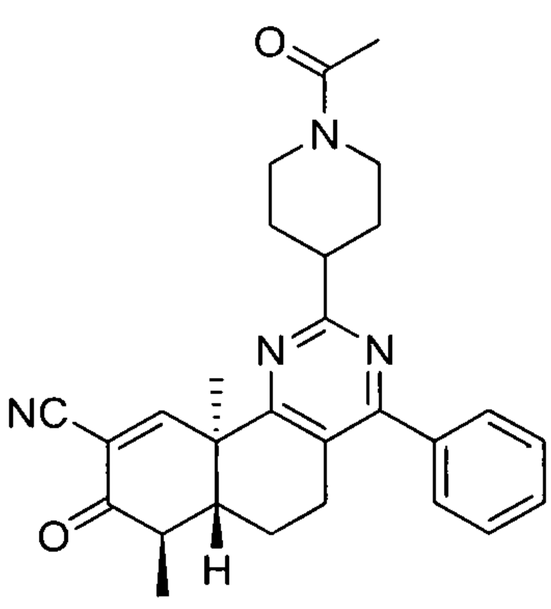
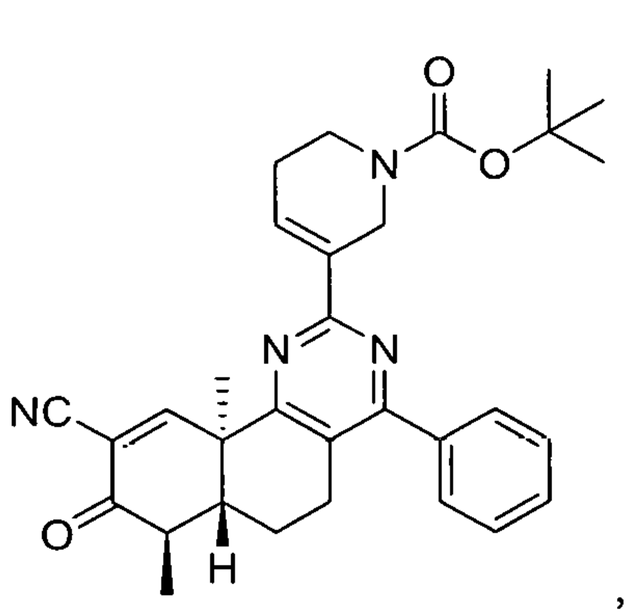
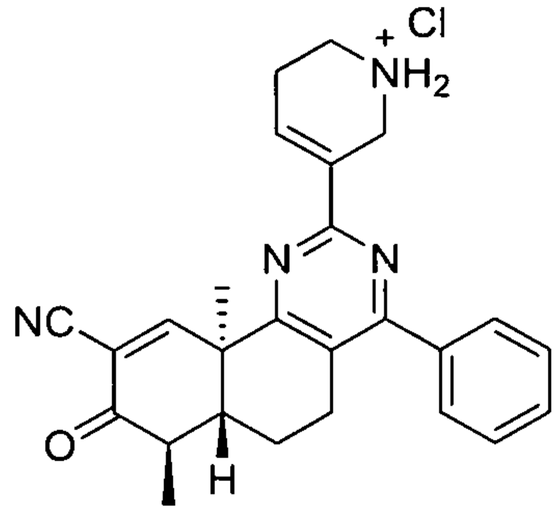
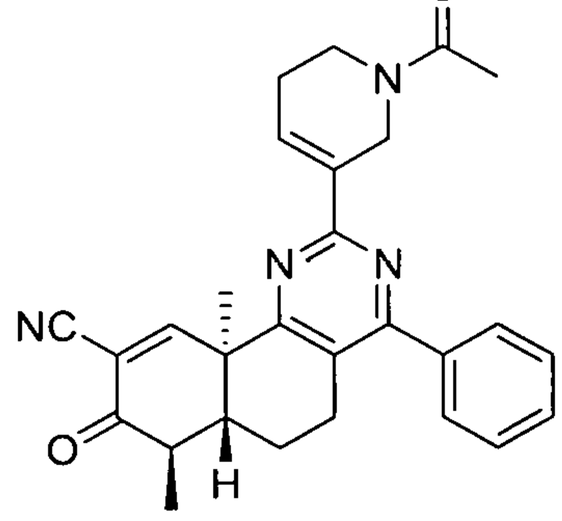
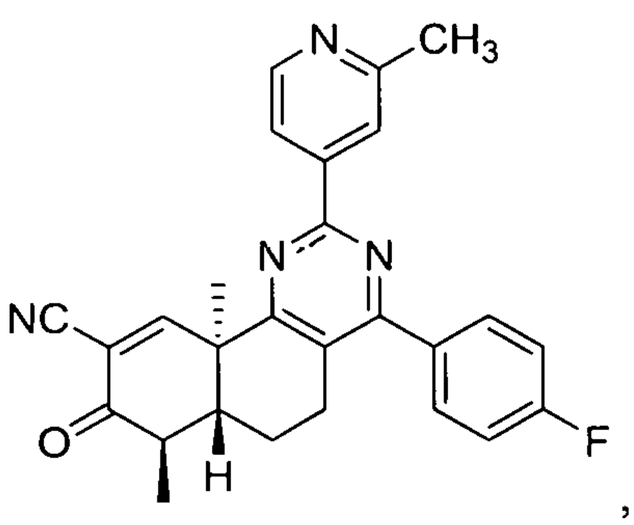
145. The compound according to any one of claims 1-8 and 13-77, wherein R_5 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$.

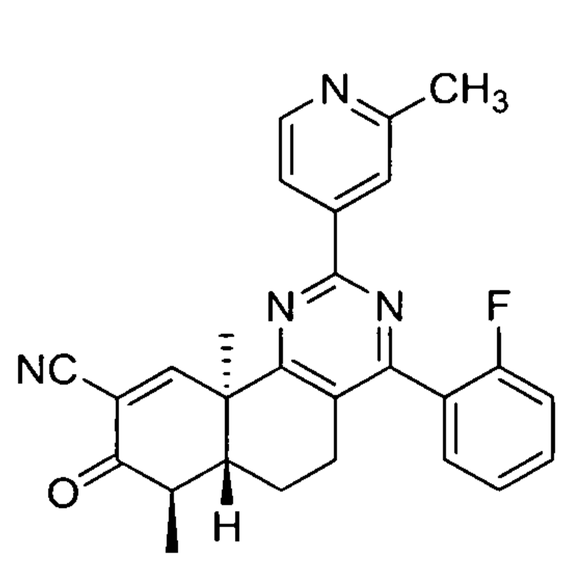
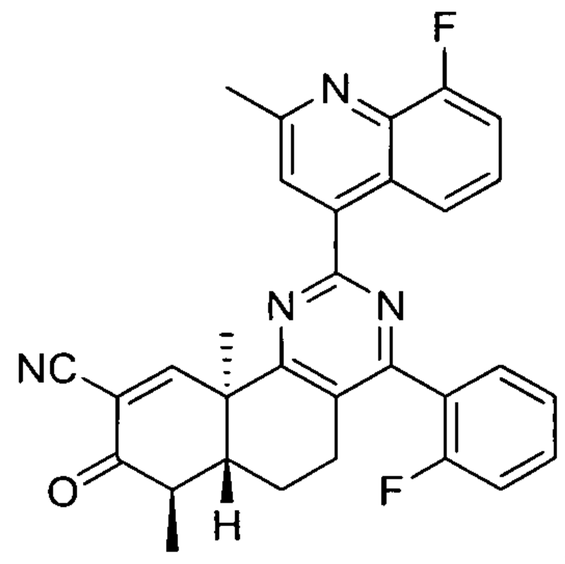
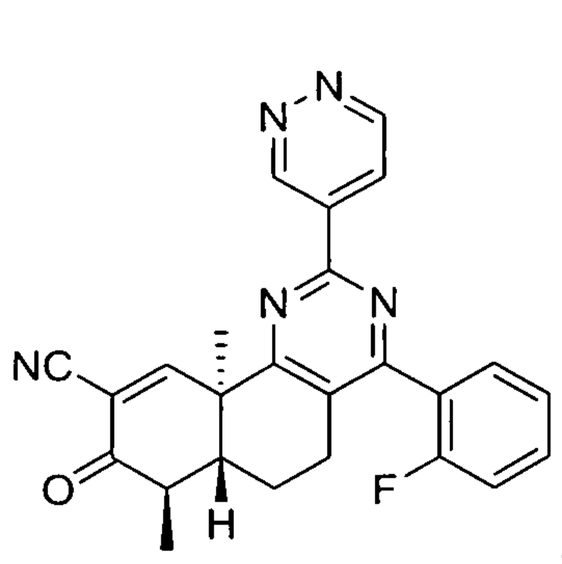
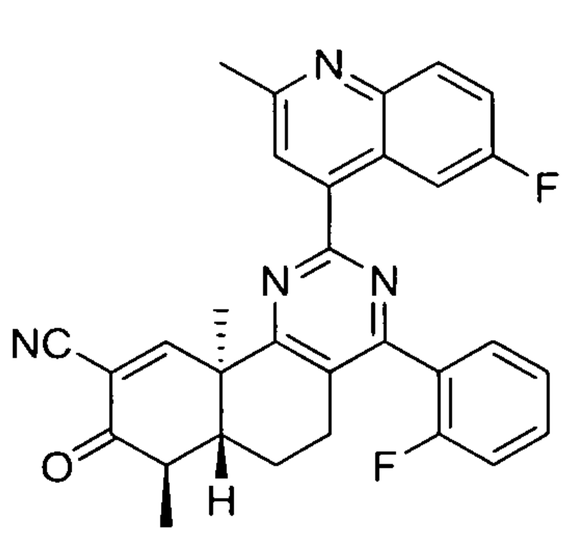
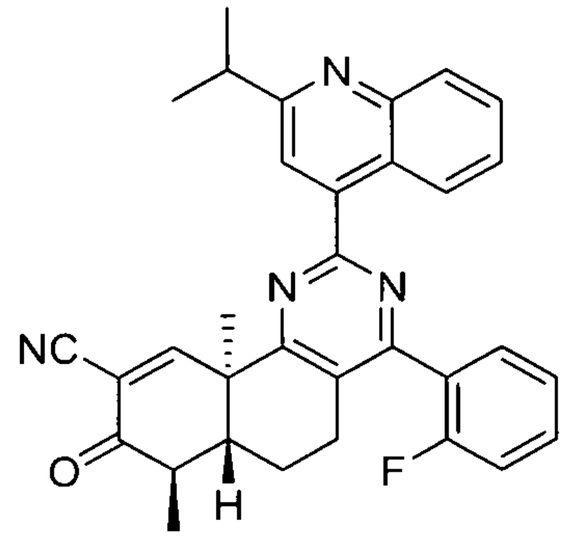
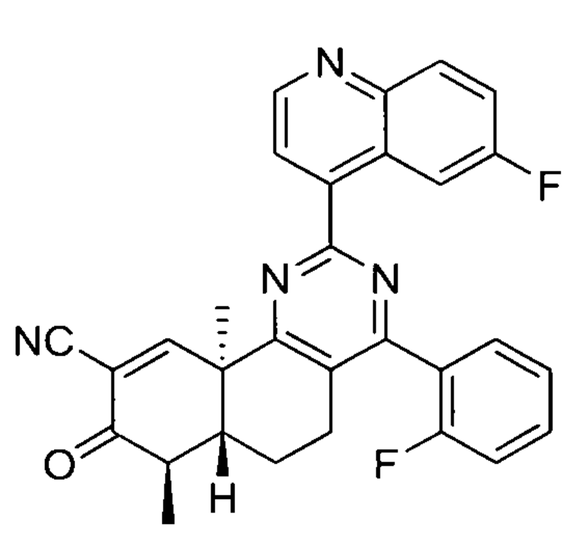
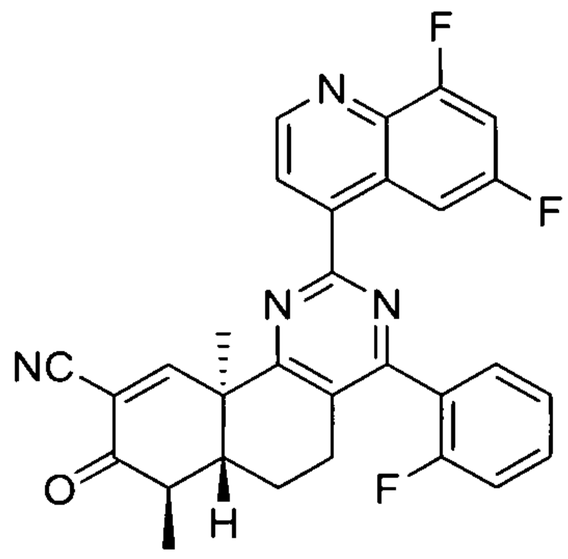
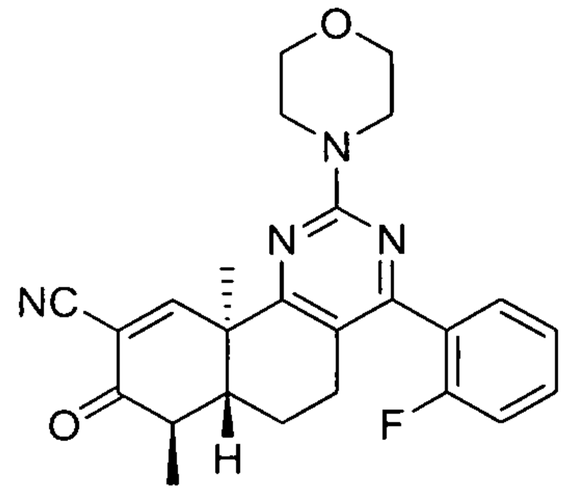
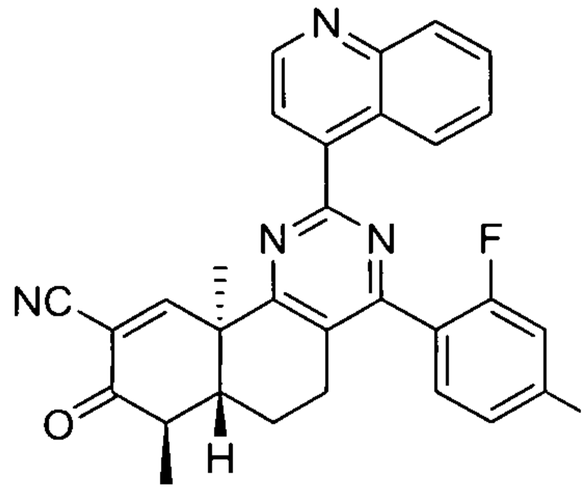
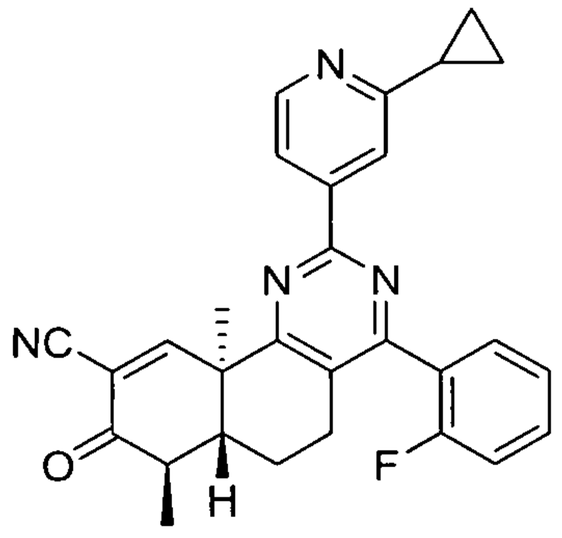
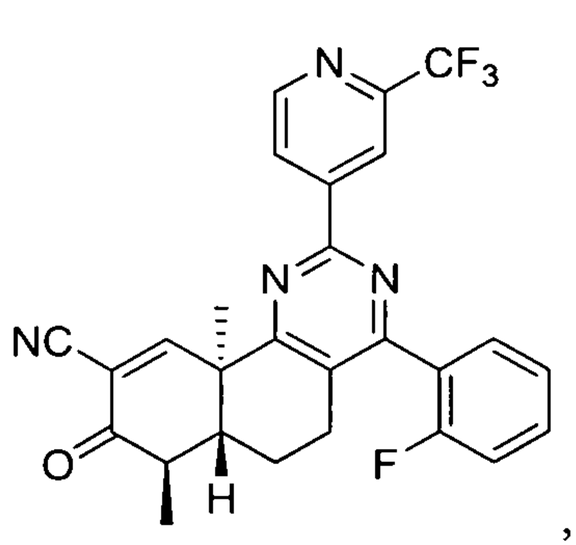
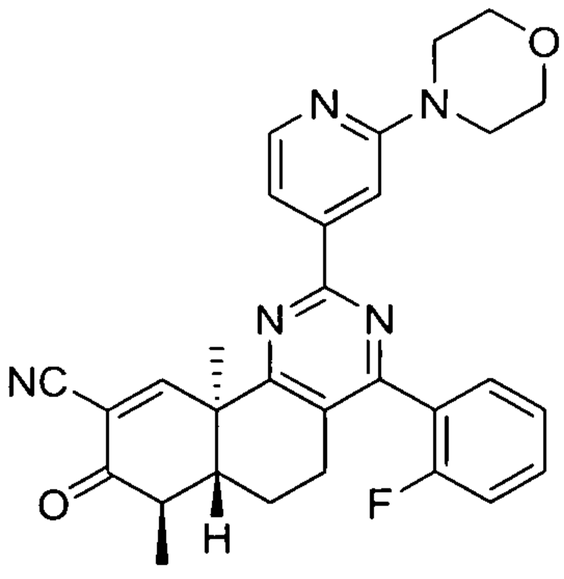
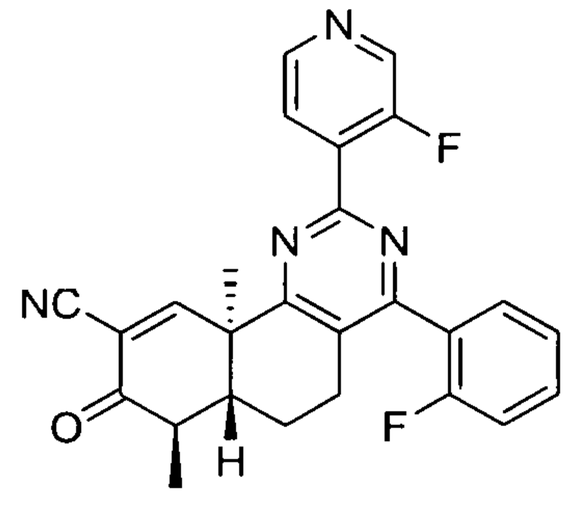
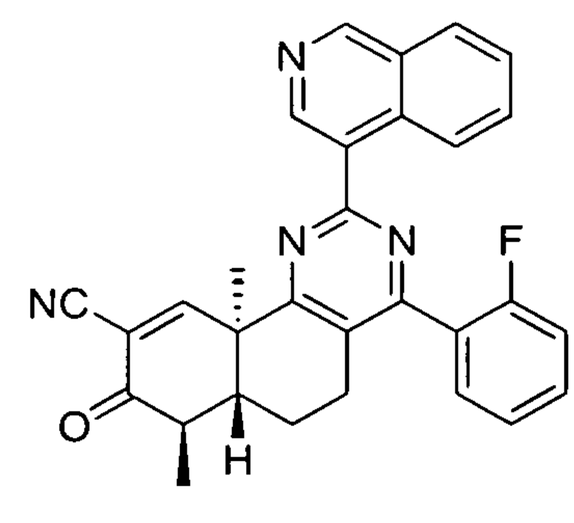
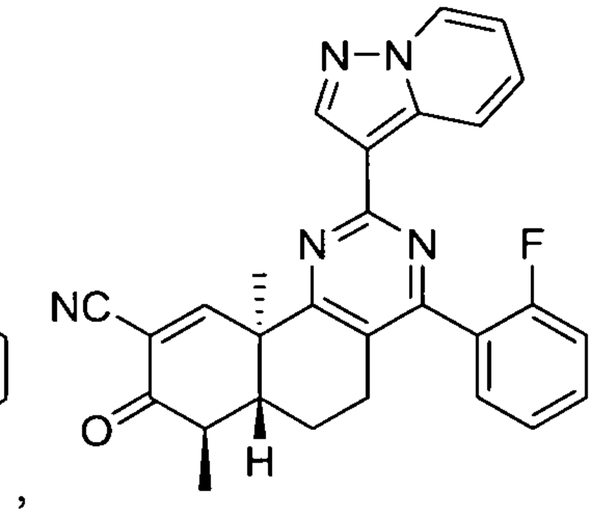
146. The compound of claim 145, wherein R_5 is aralkyl$_{(C\leq 12)}$.

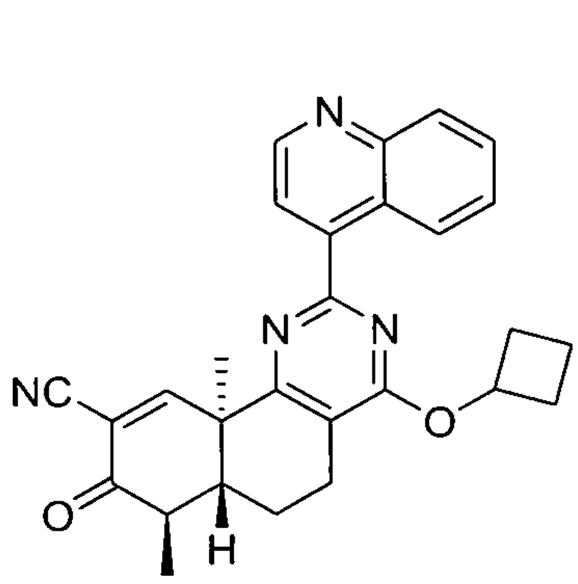
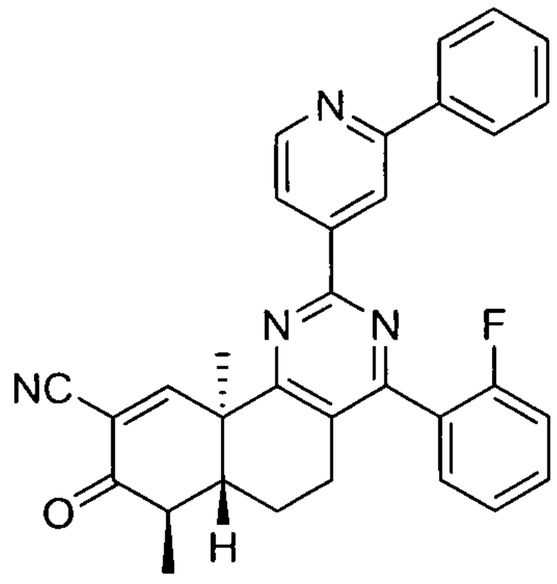
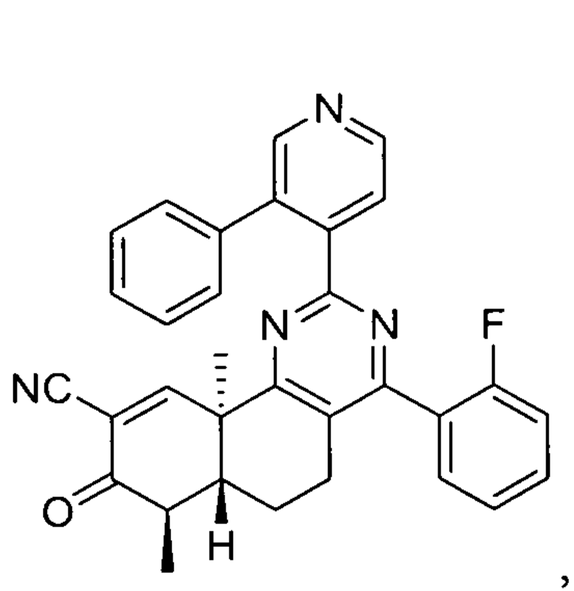
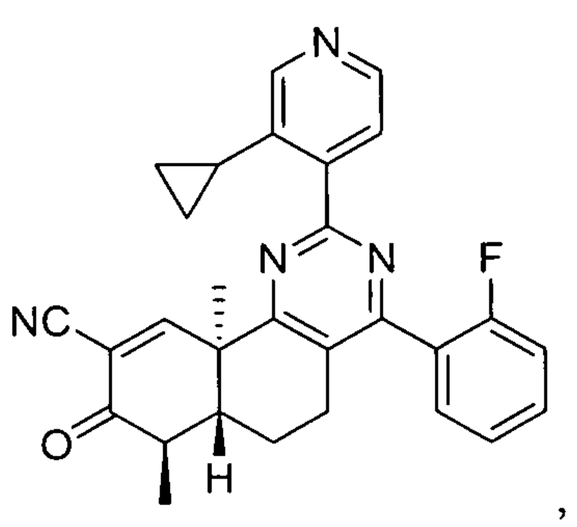
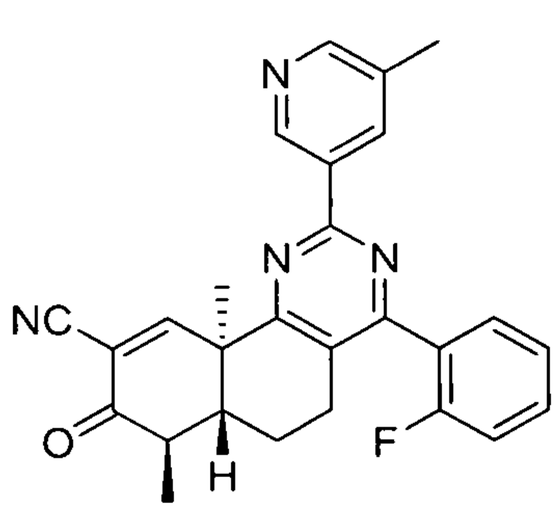
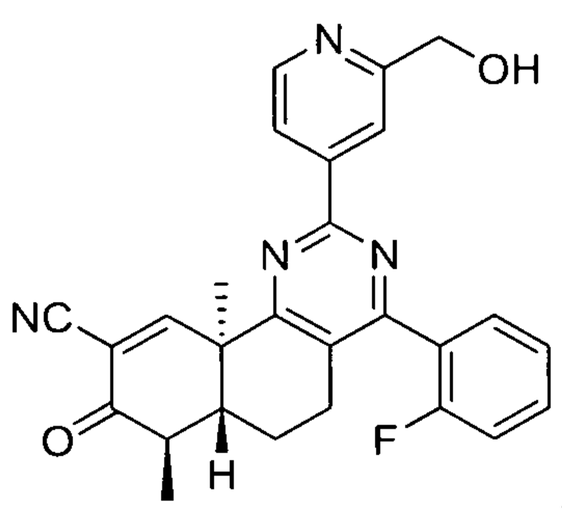
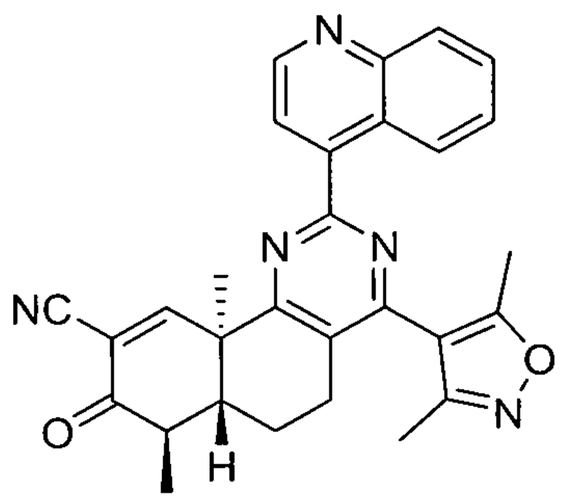
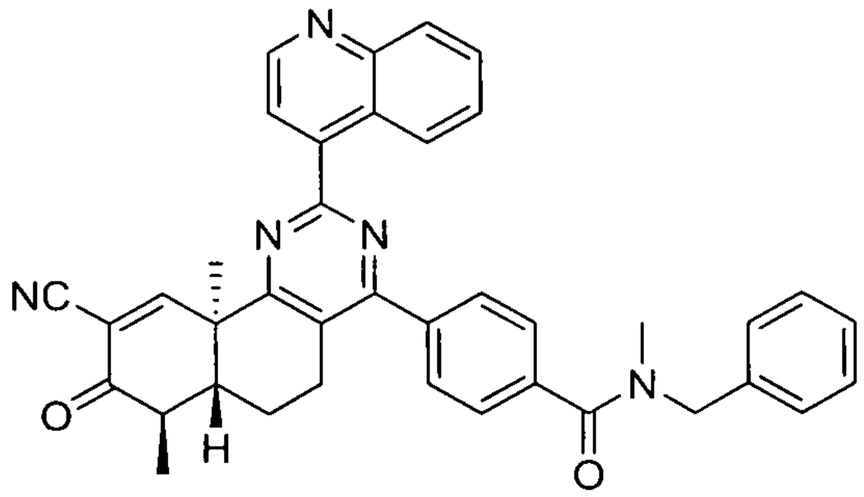
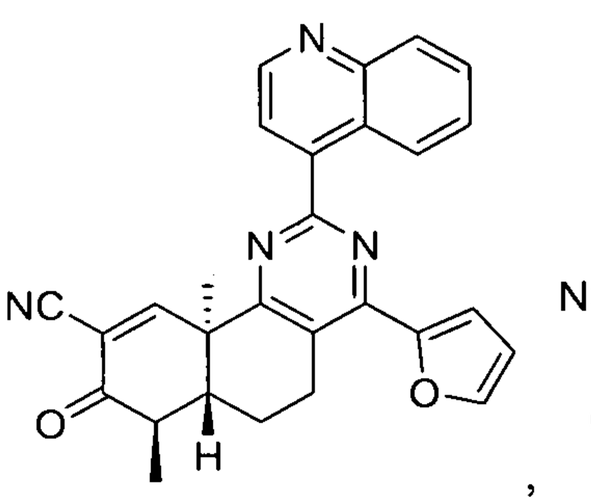
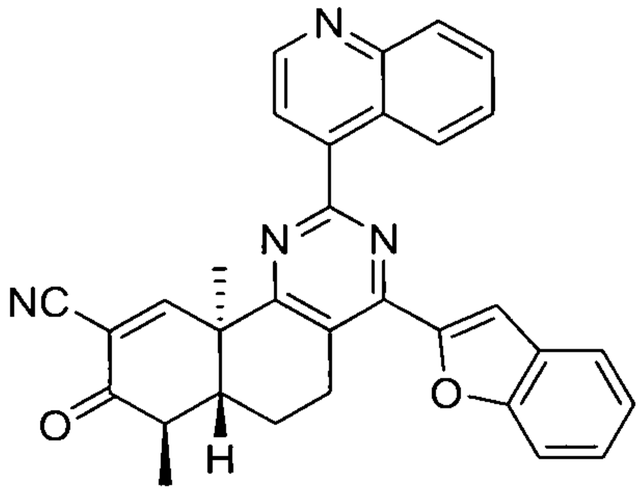
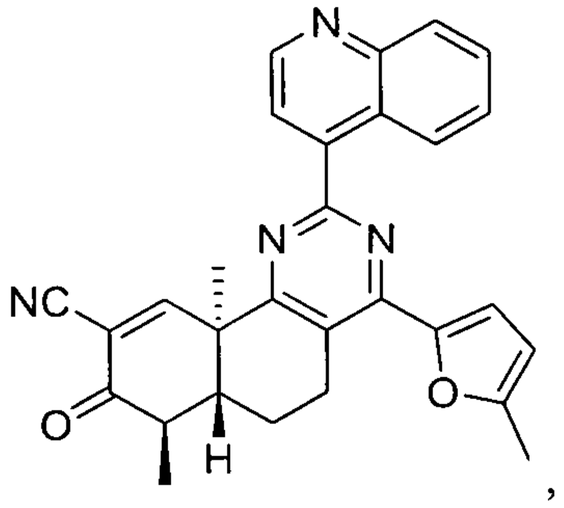
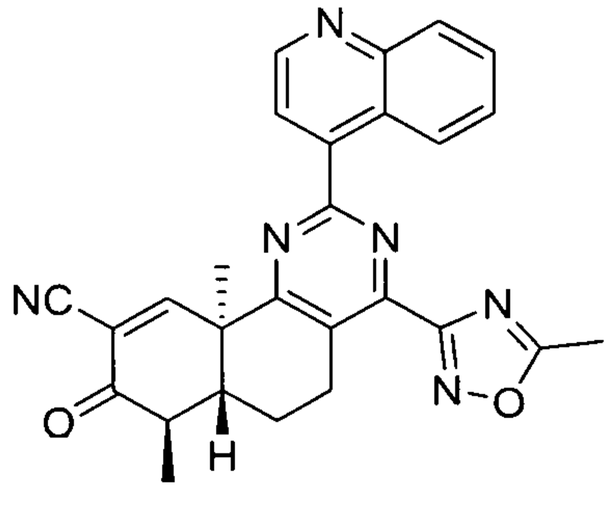
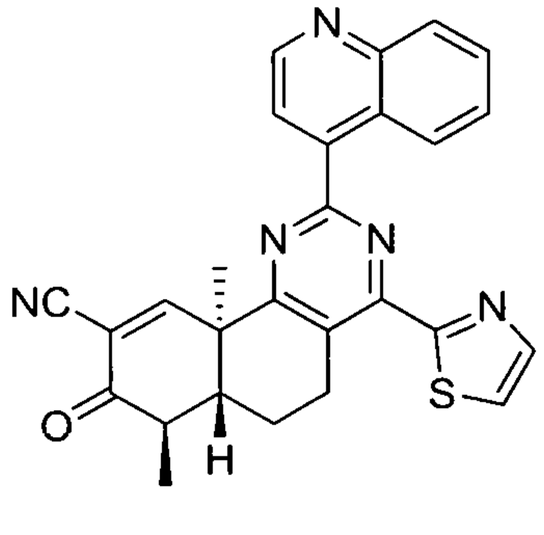
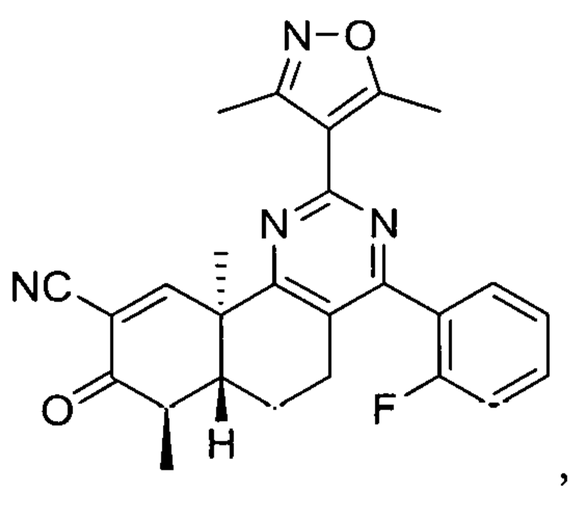
147. The compound of claim 146, wherein R_5 is benzyl.

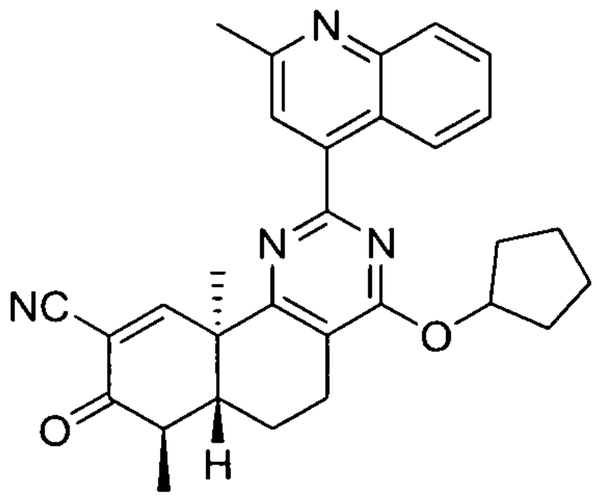
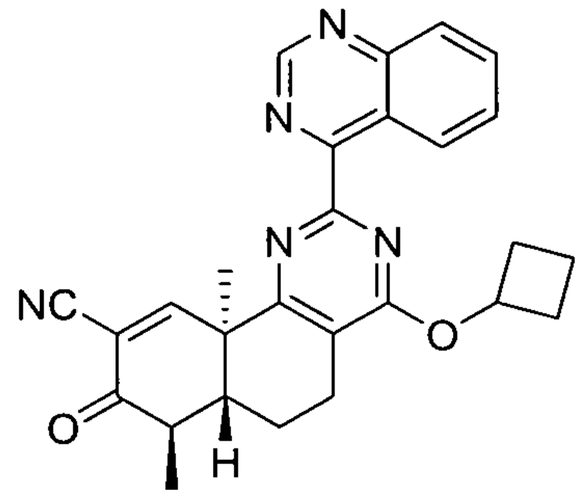
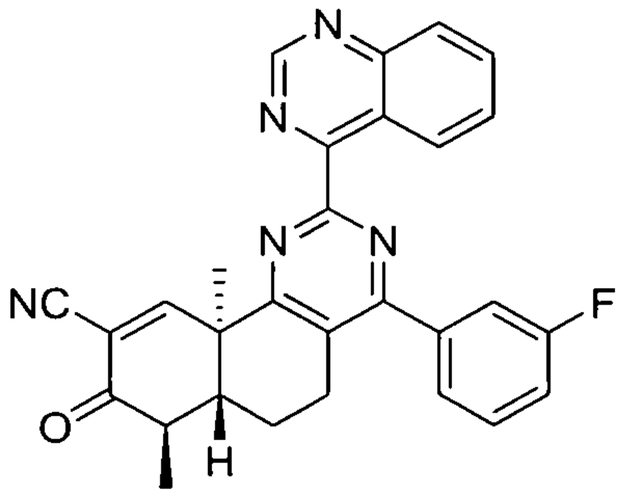
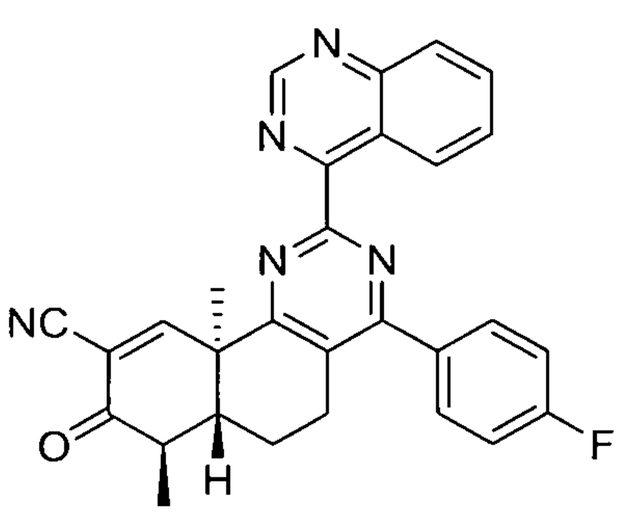
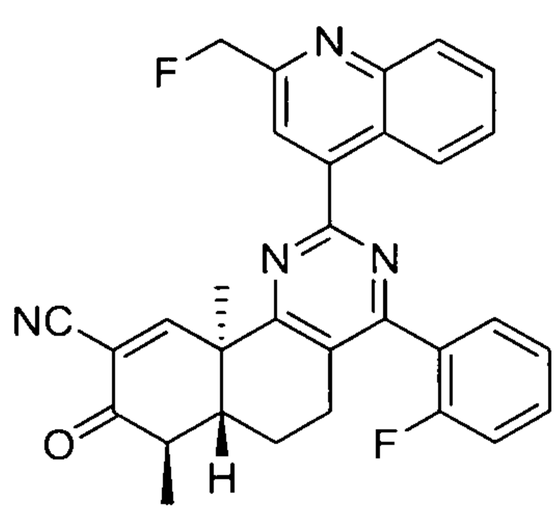
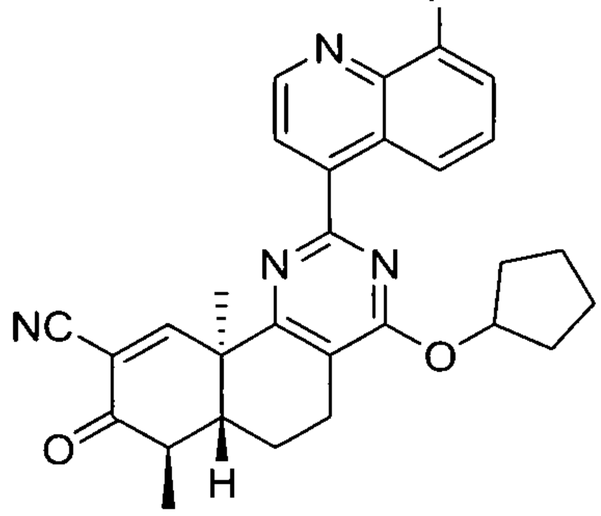
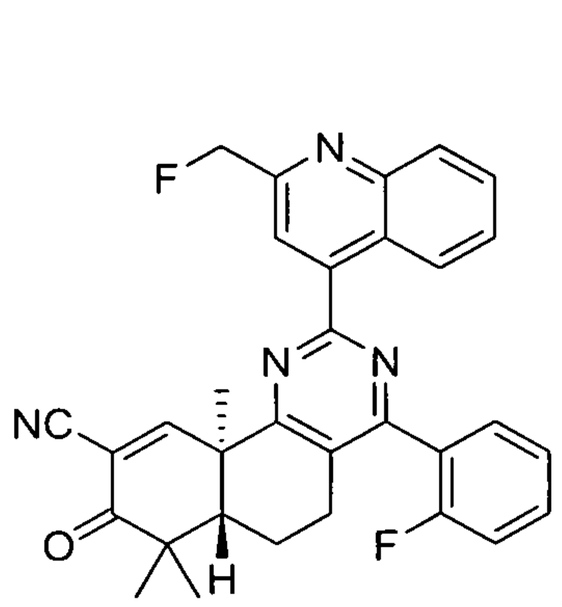
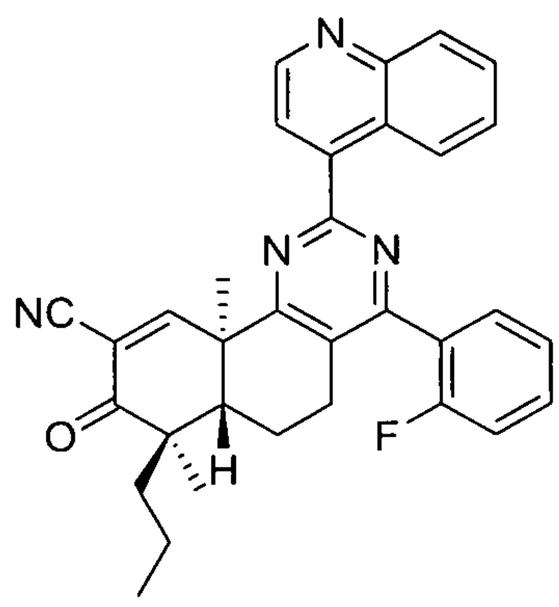
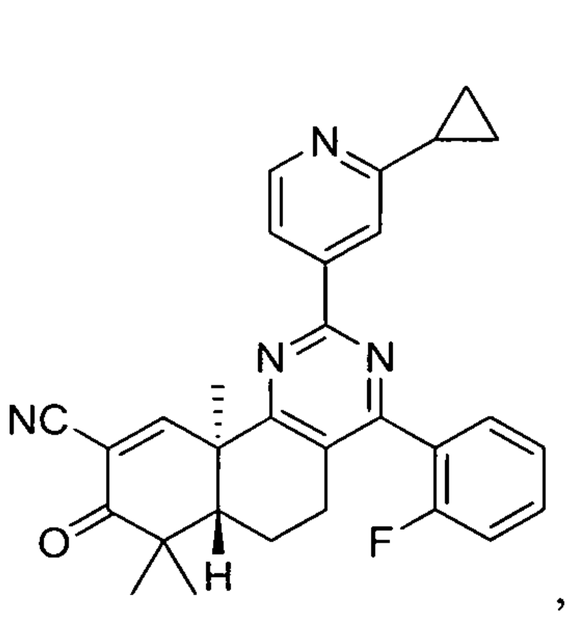
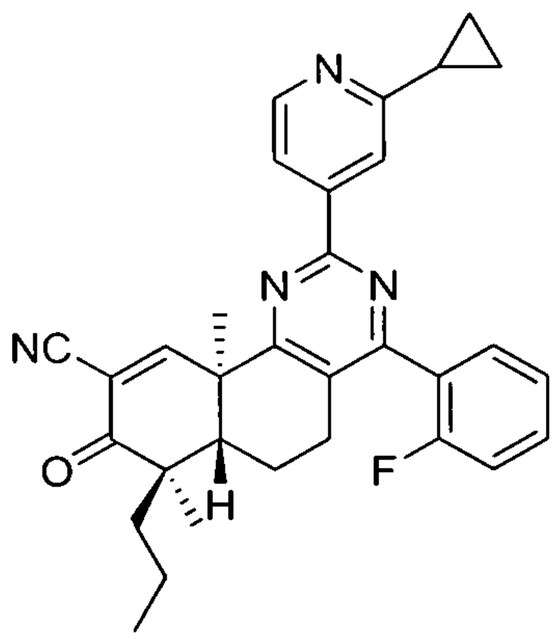
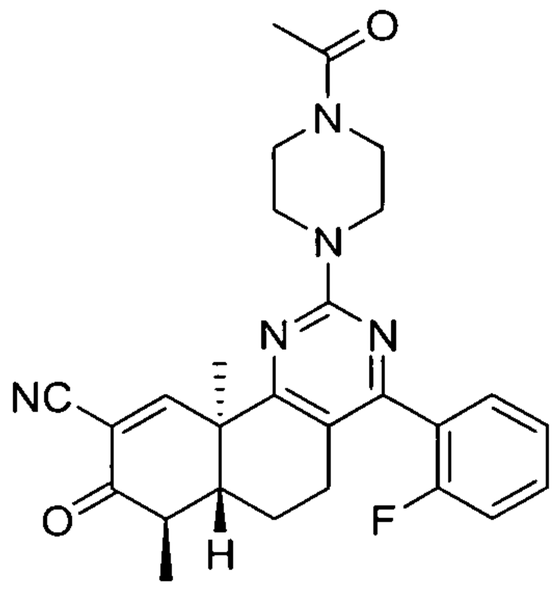
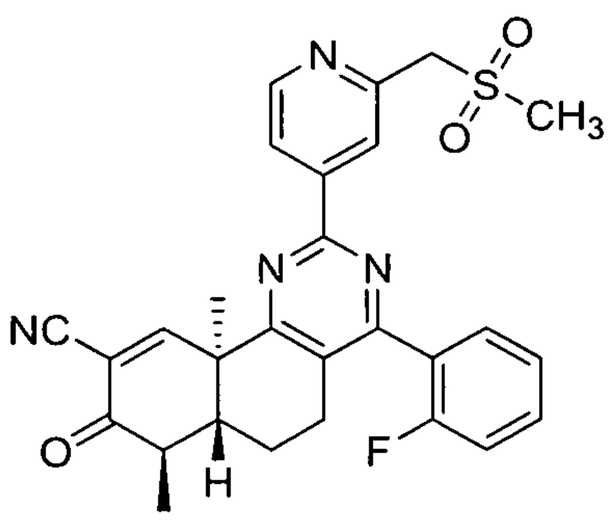
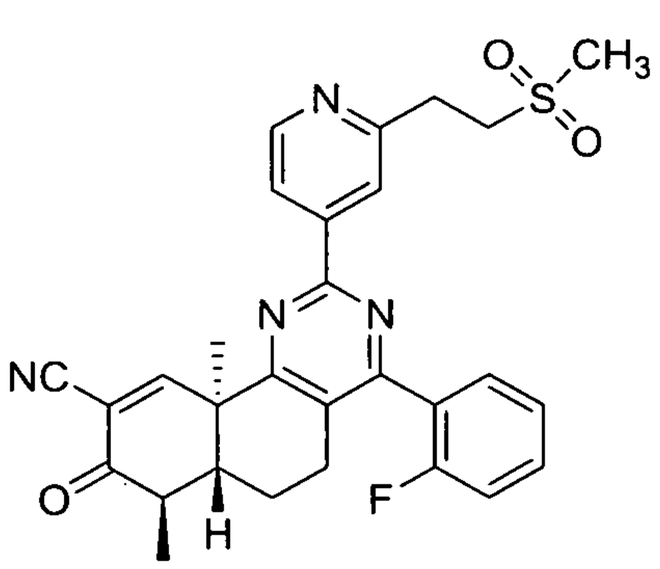
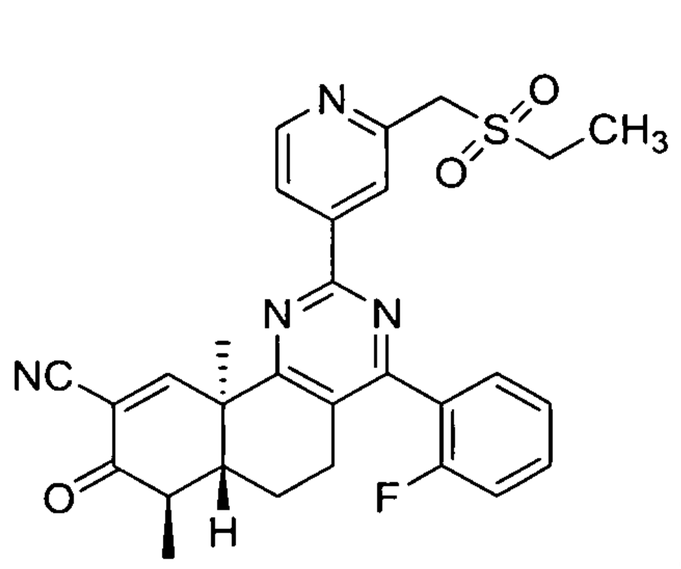
148. The compound according to any one of claims 1-12, wherein the compound is further defined as:

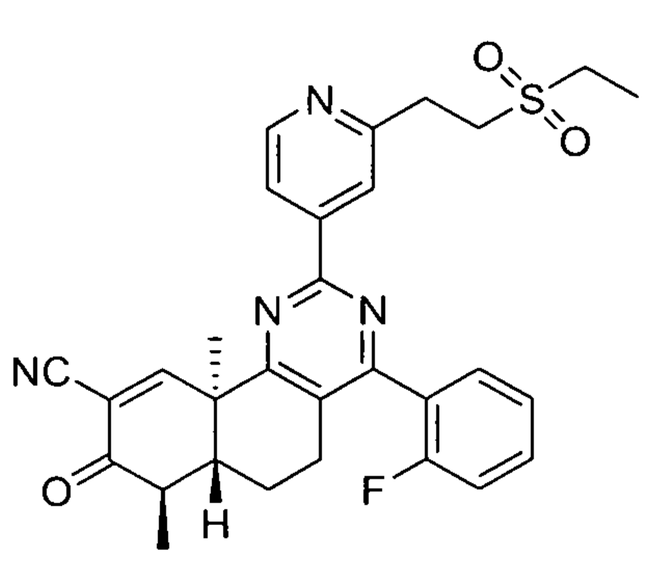
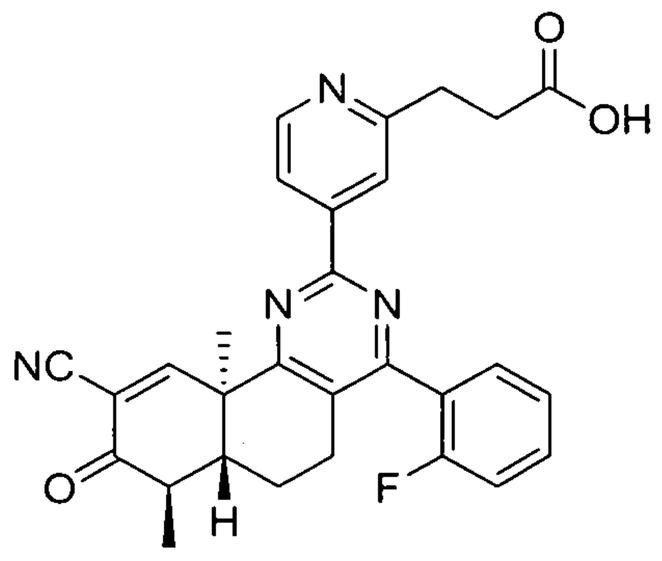
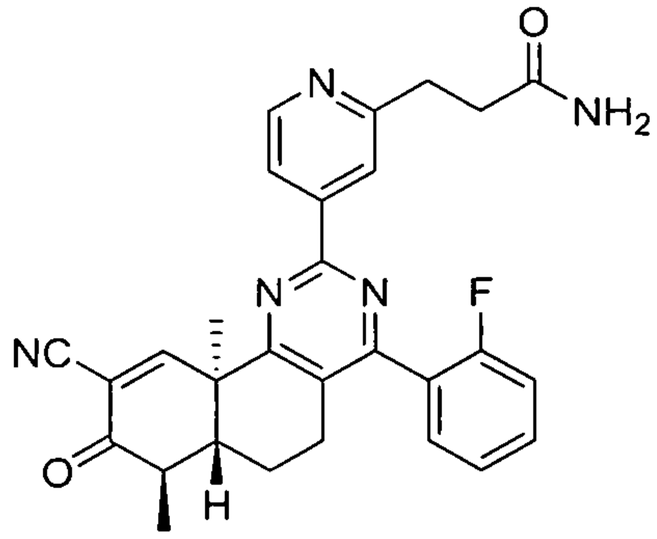
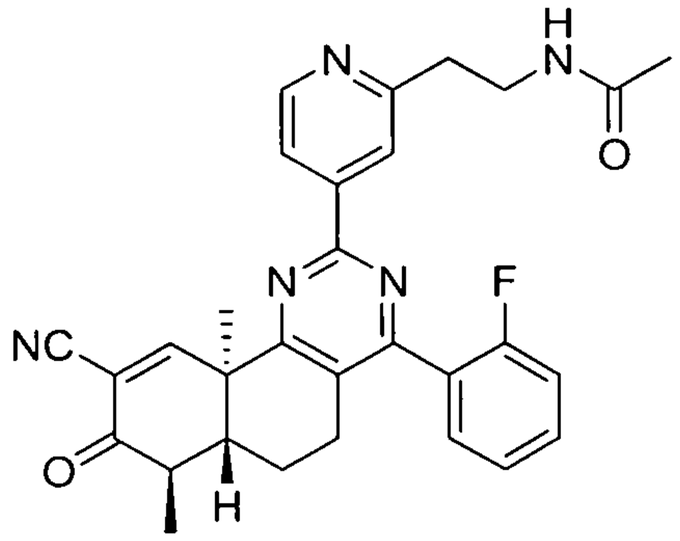
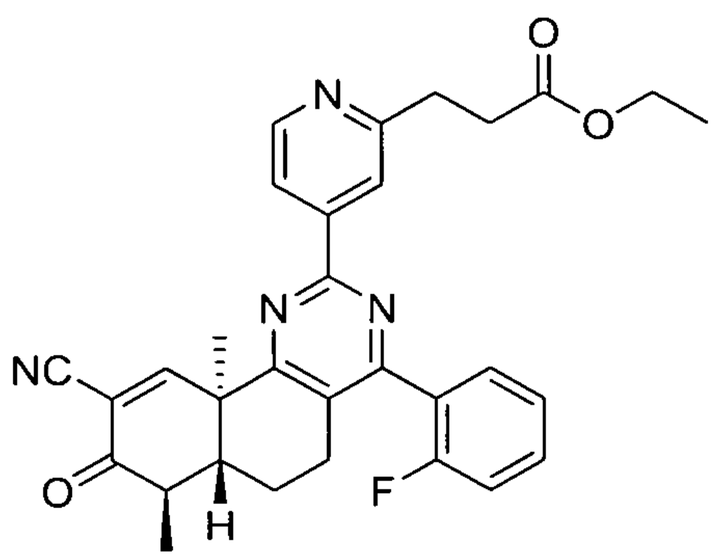
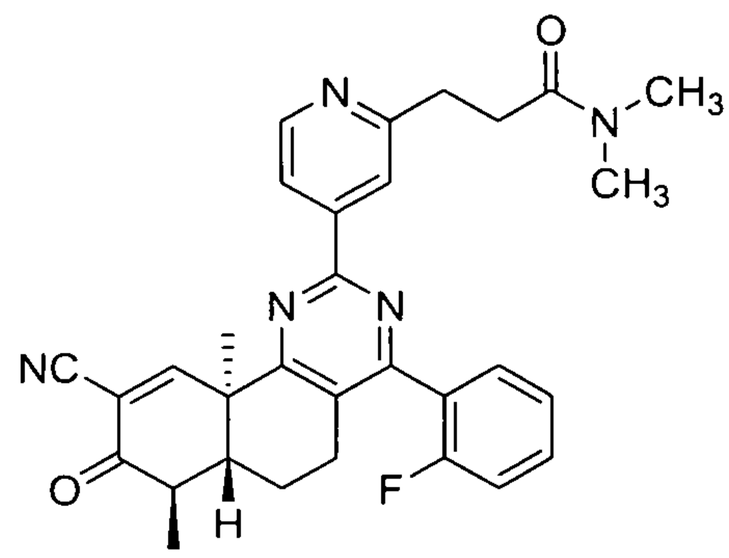
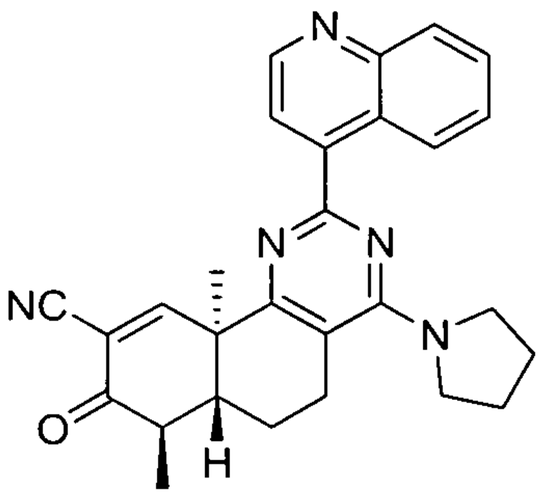
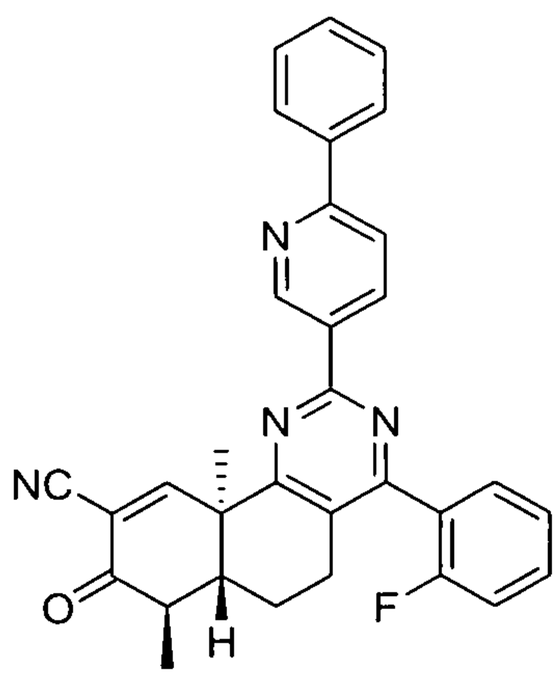
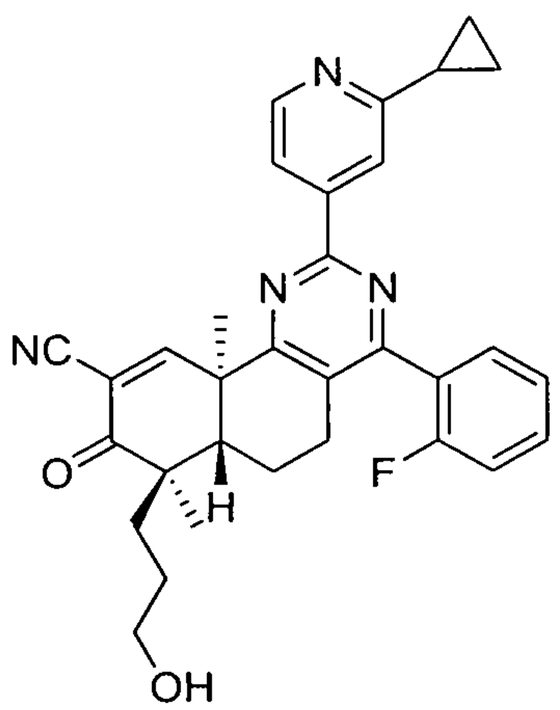

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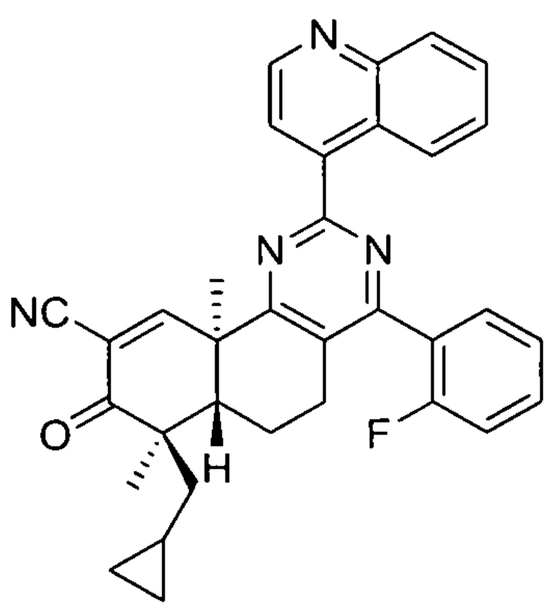
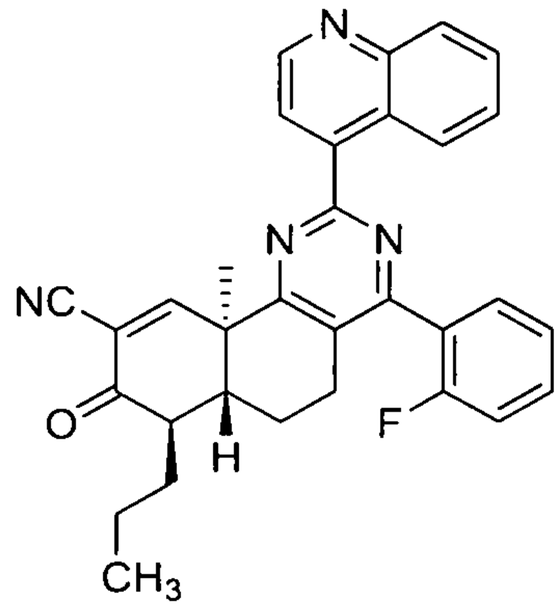
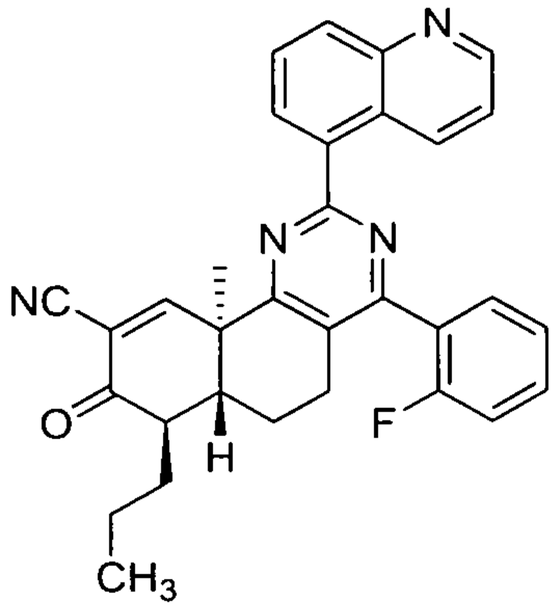
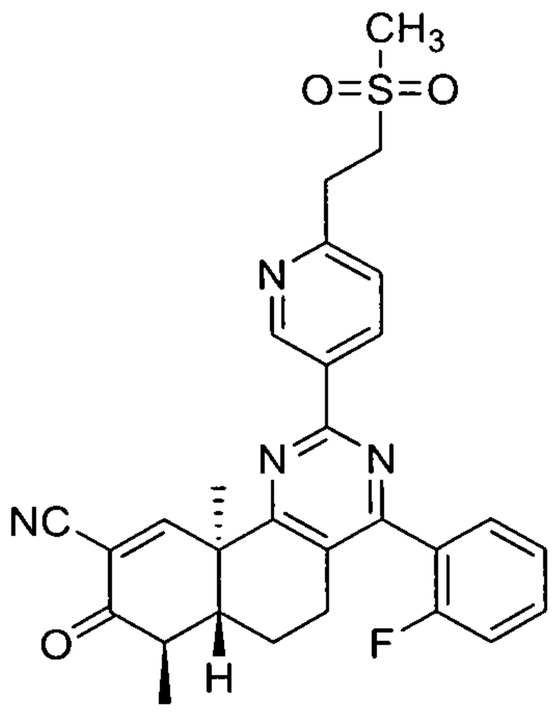
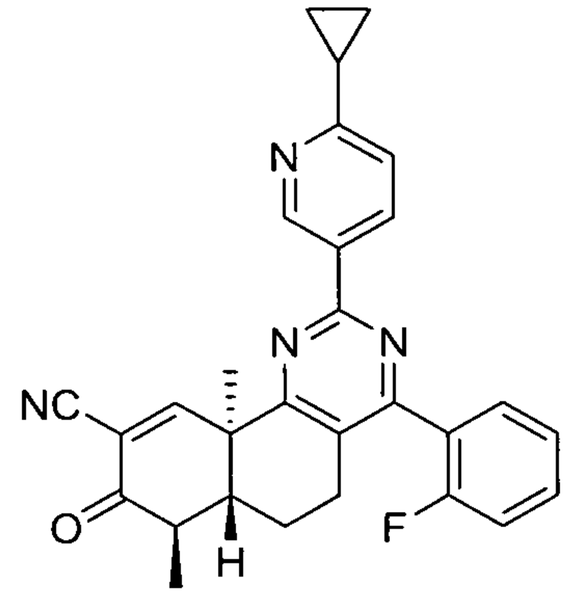
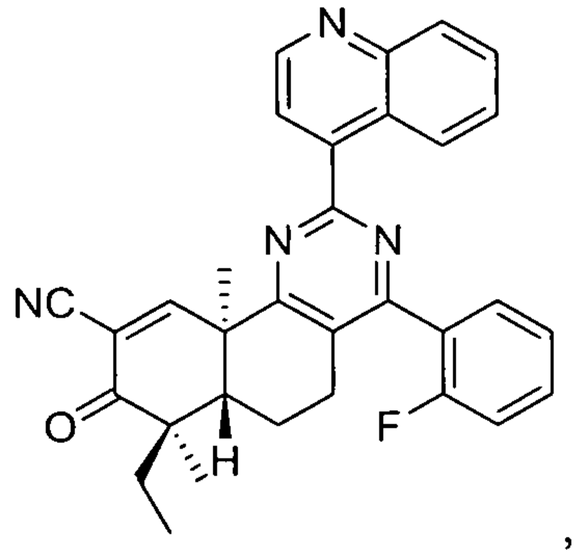
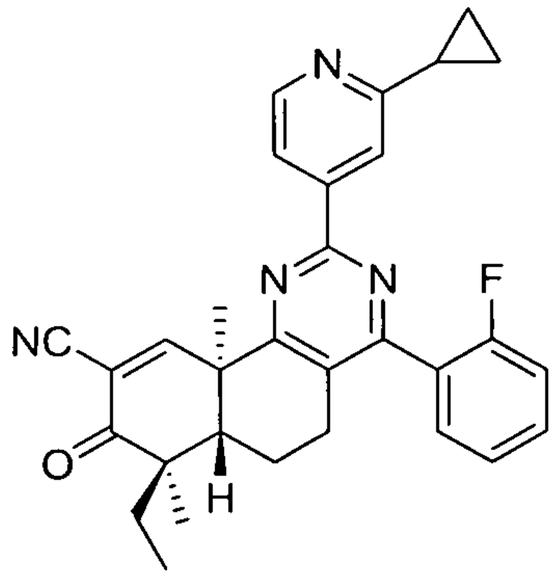
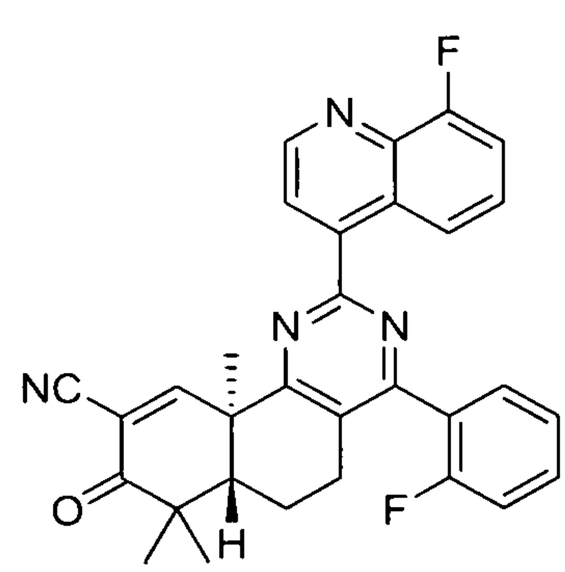
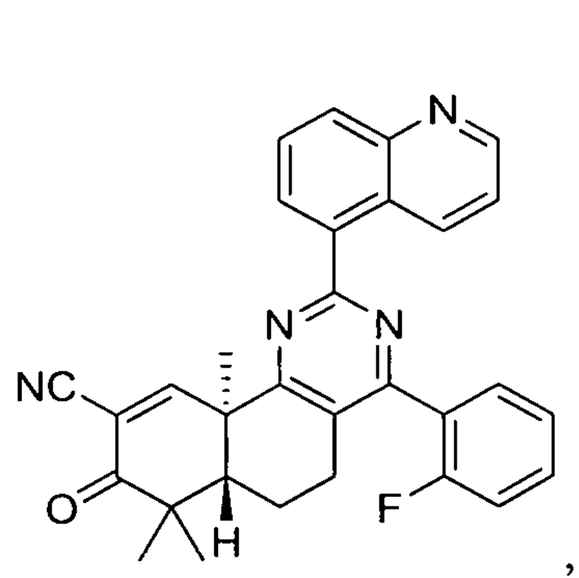
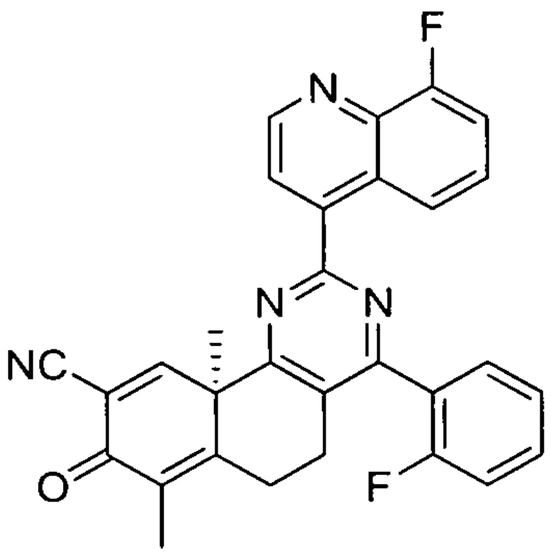
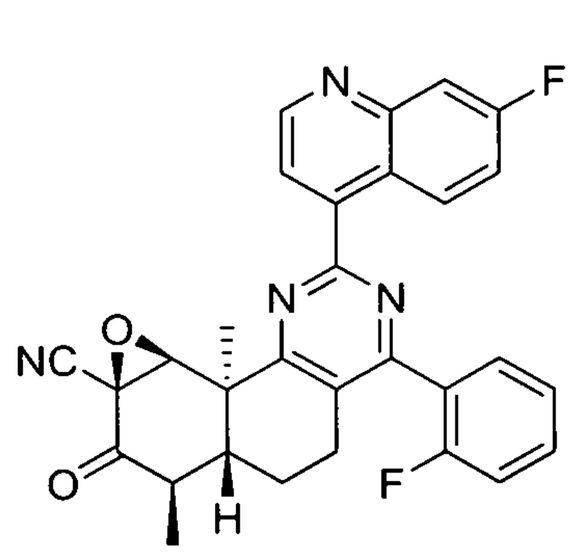
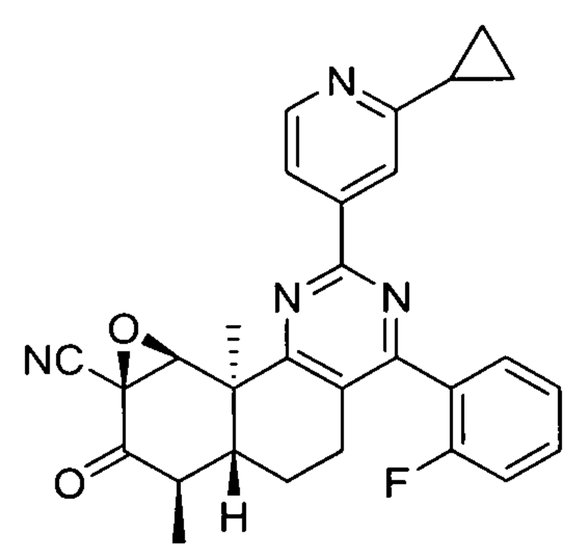

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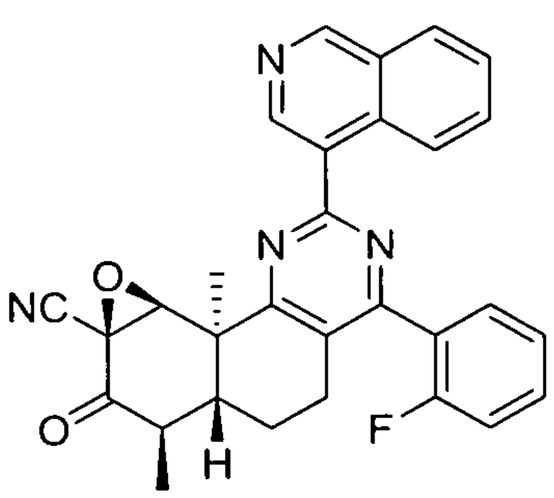
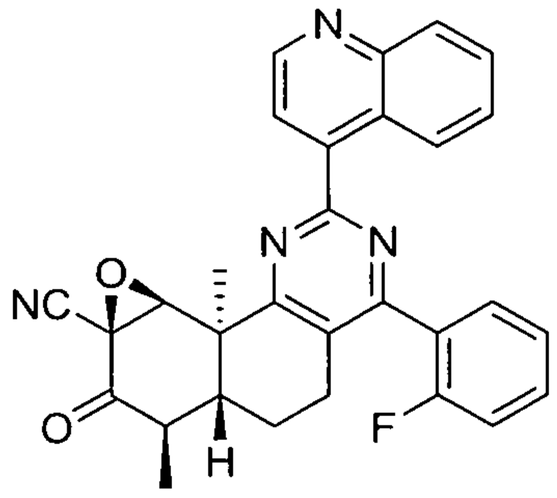
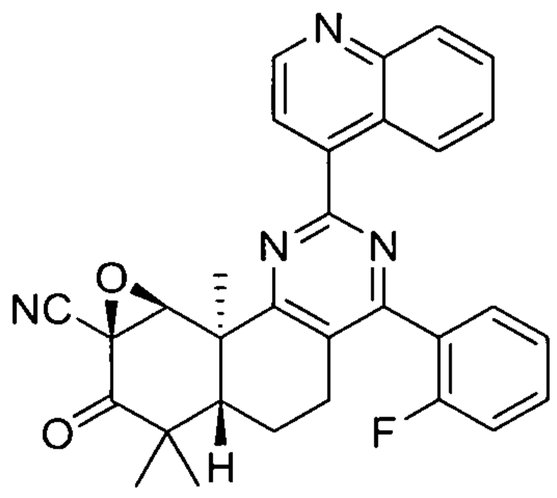
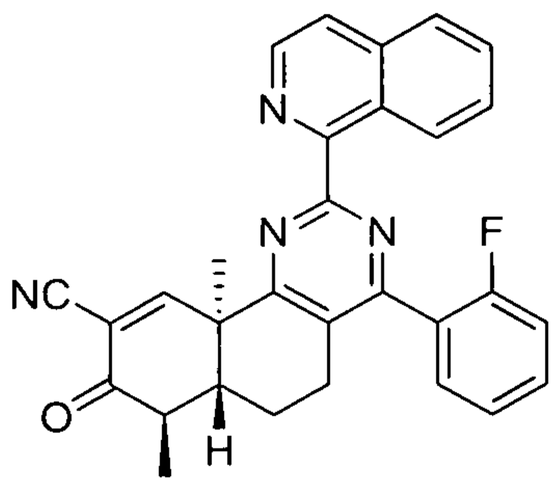
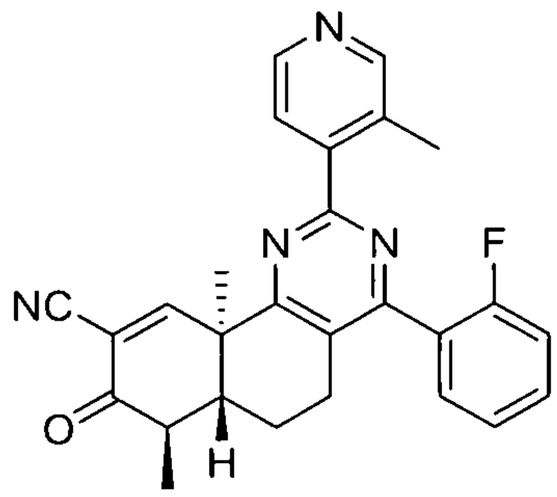
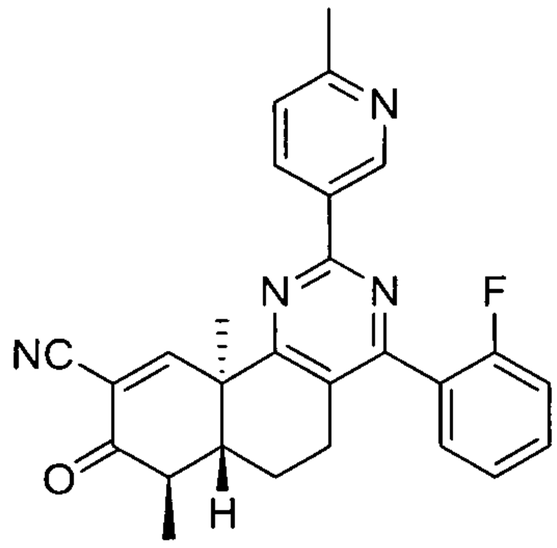
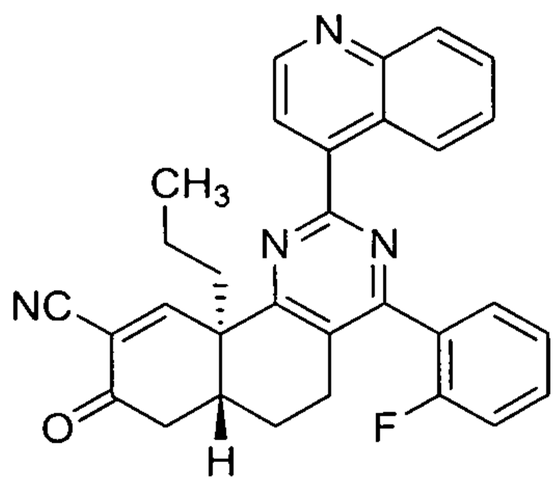
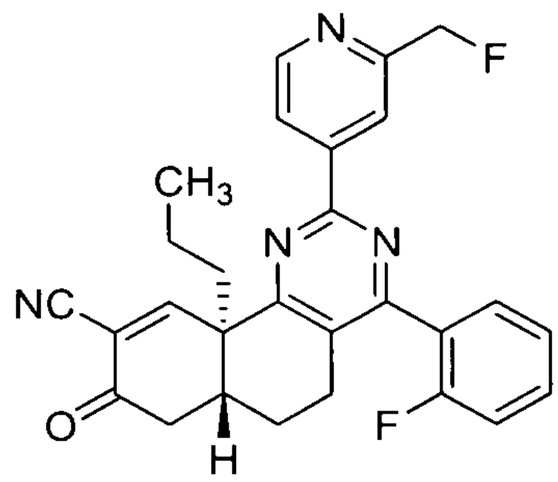
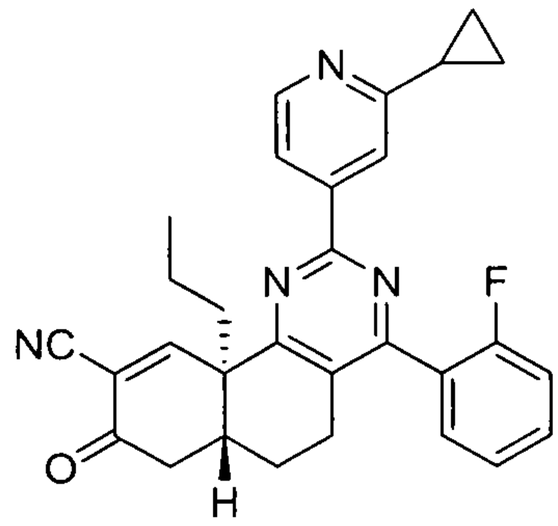
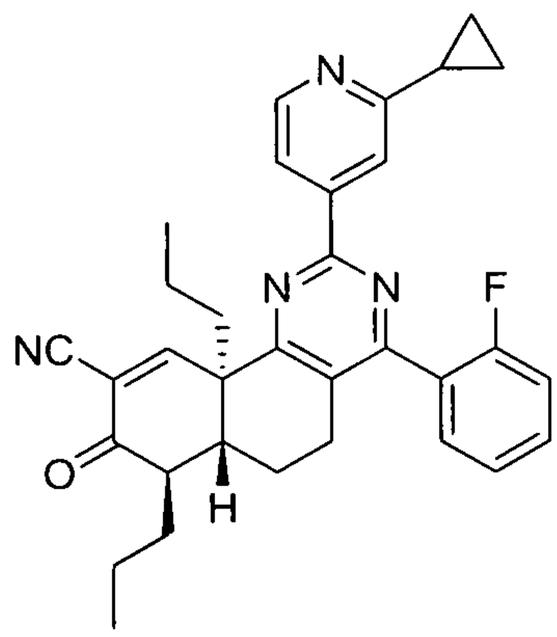
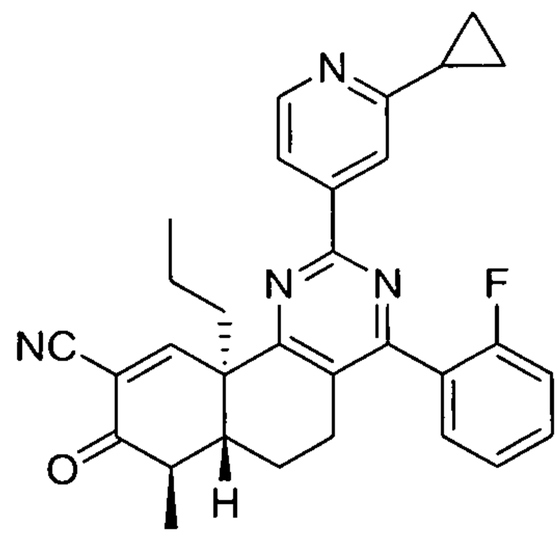
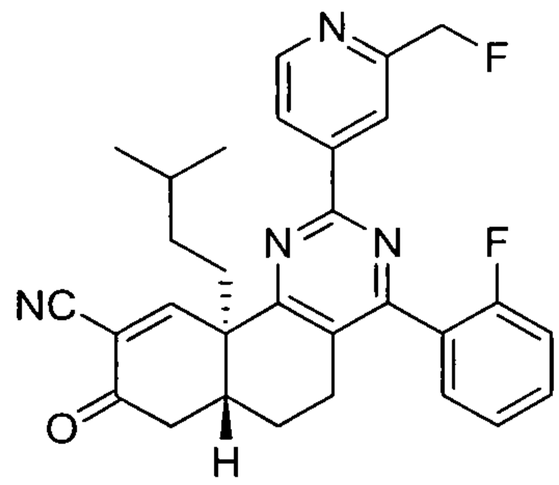
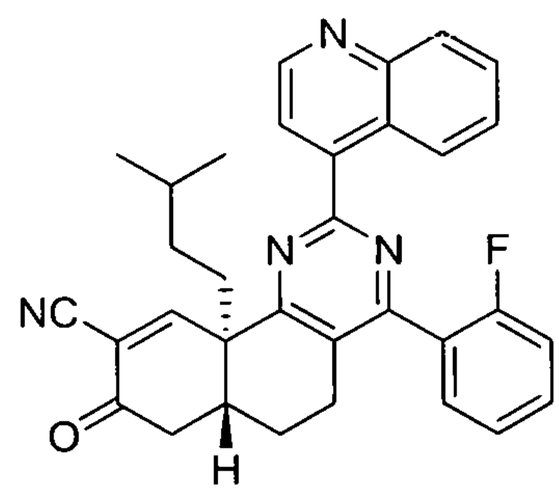
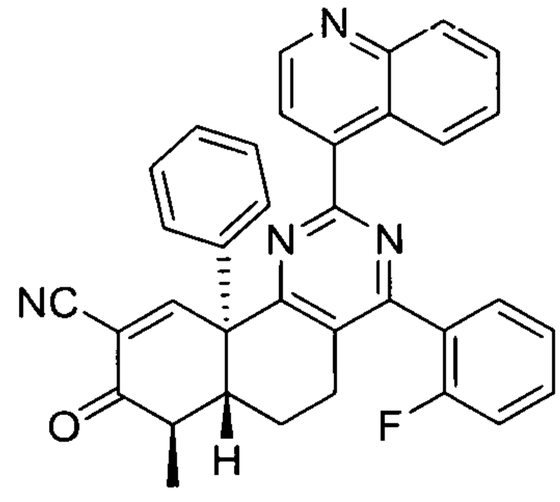
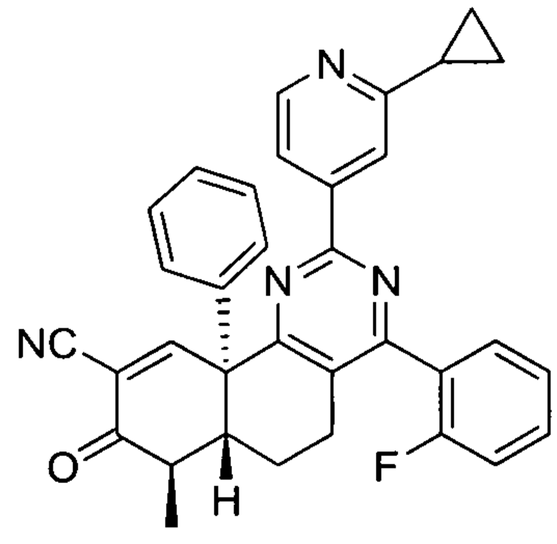

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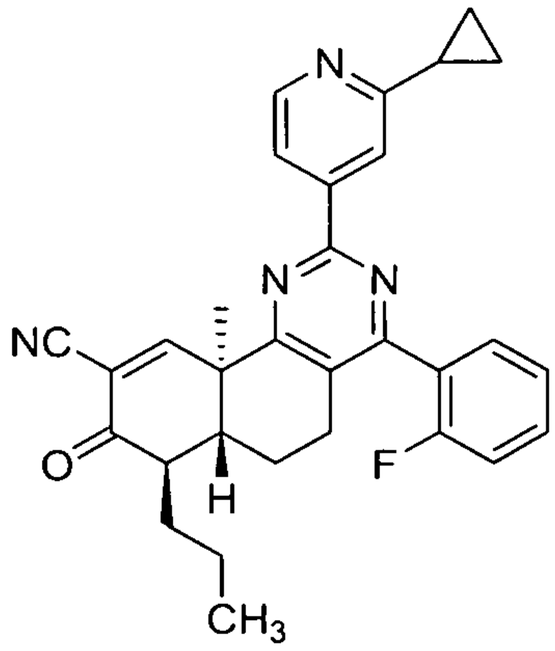
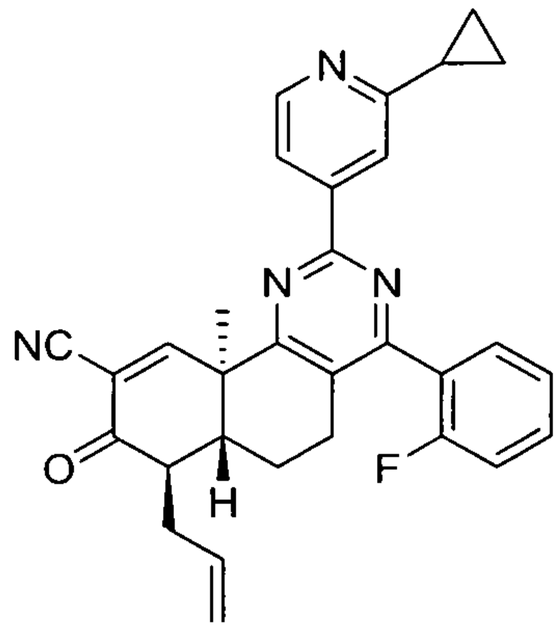
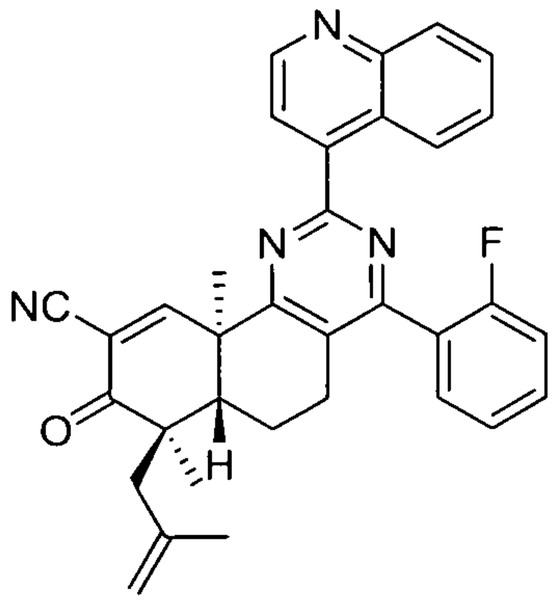
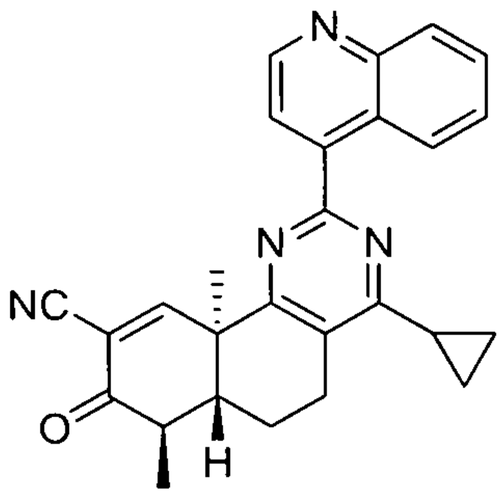
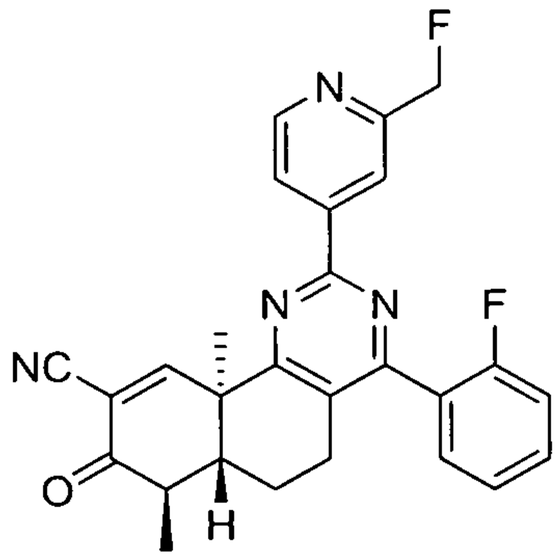
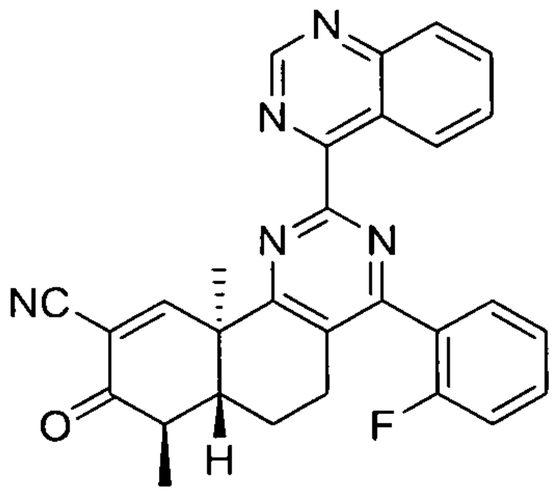
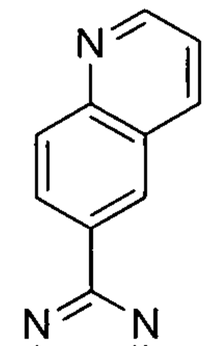
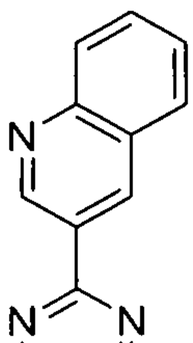
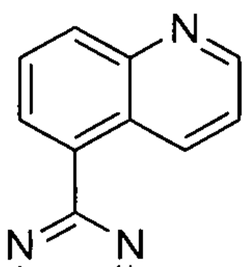
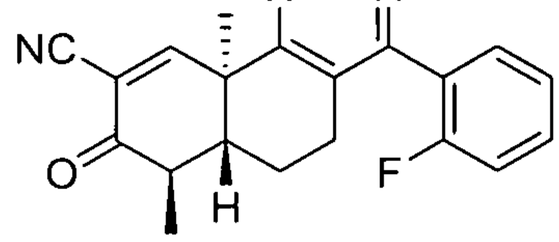
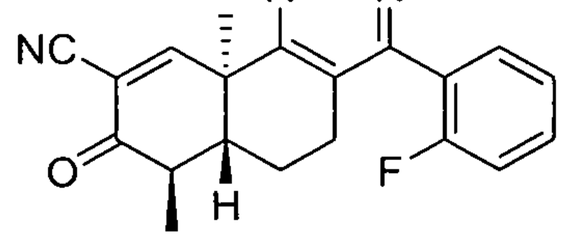
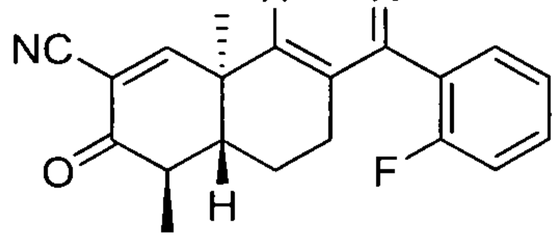
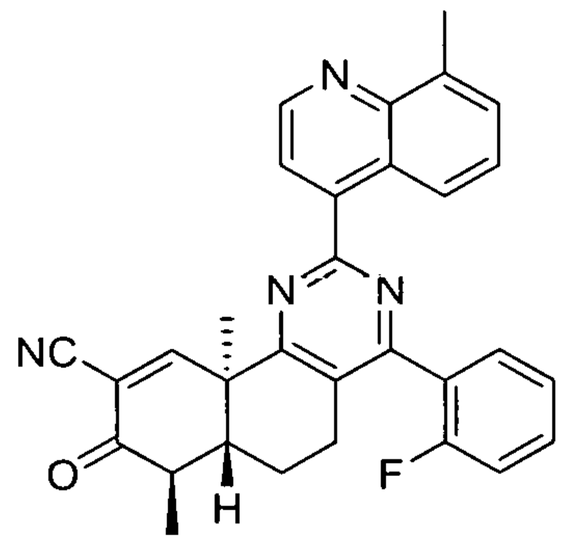
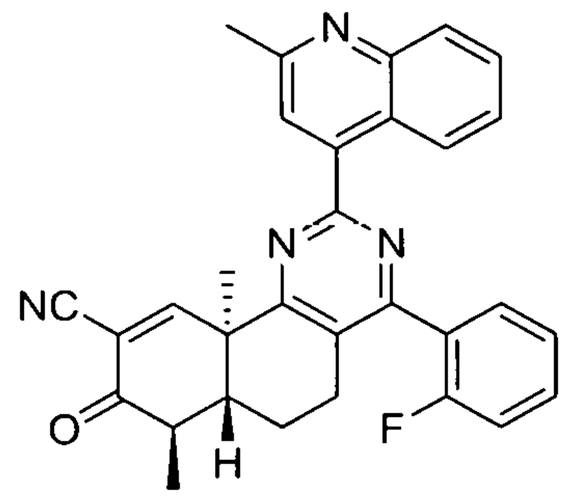
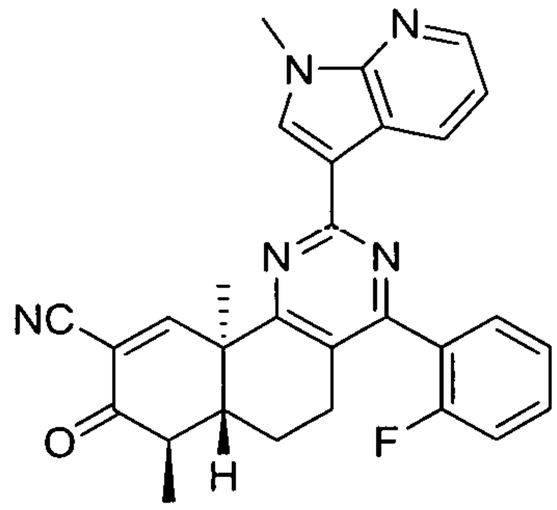

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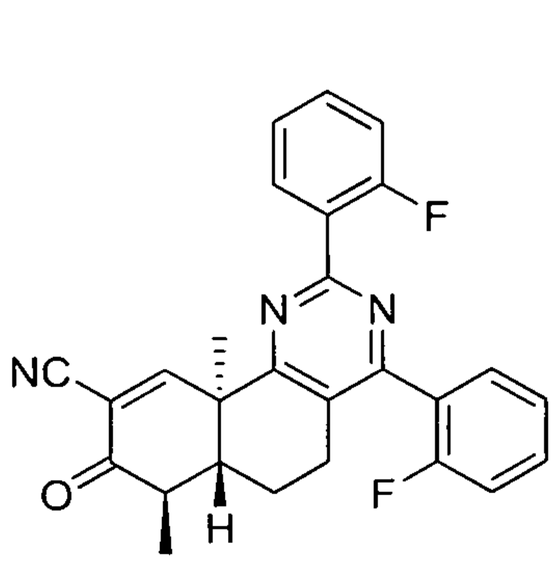
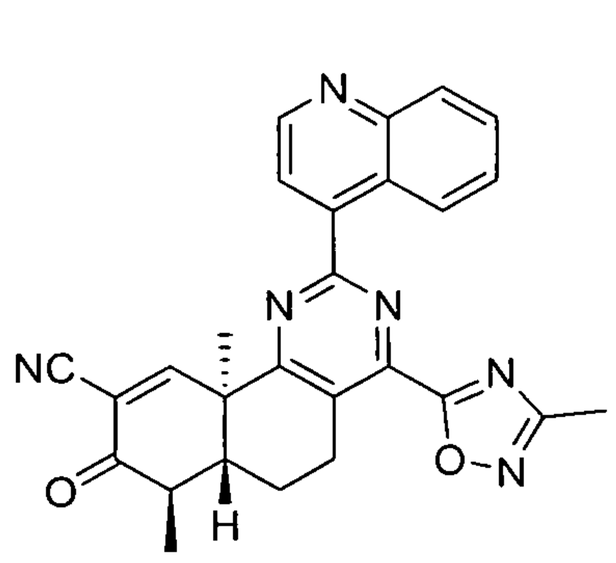
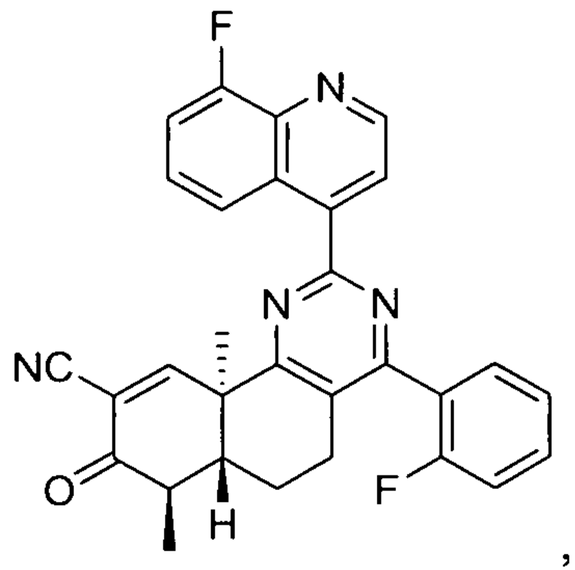
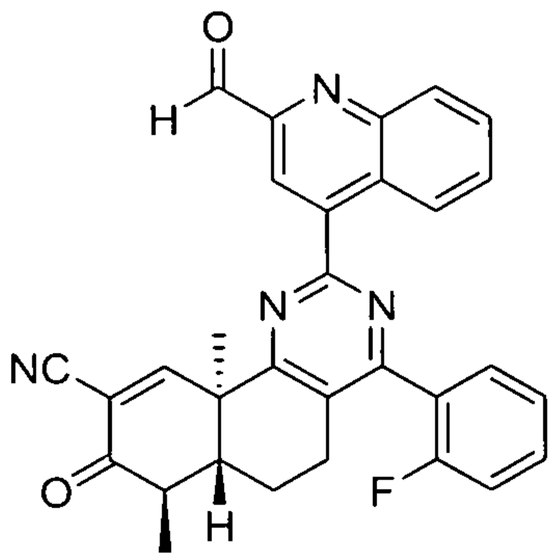
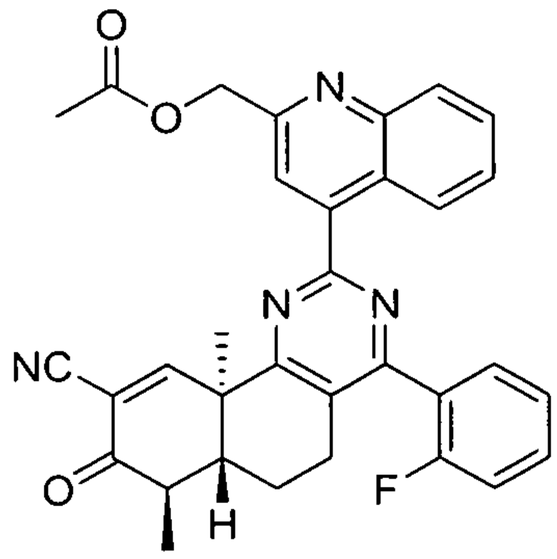
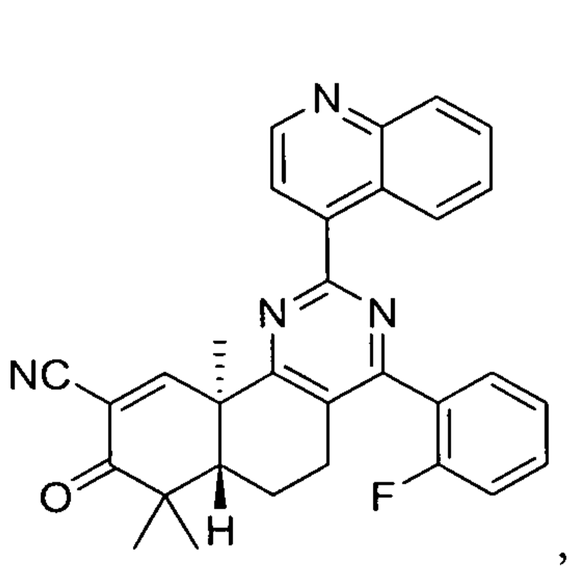
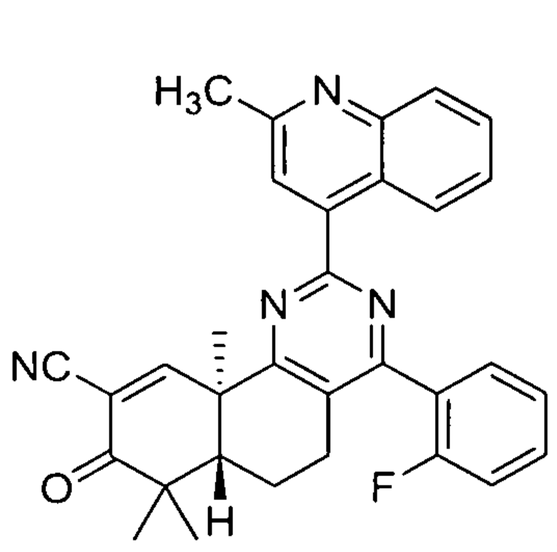
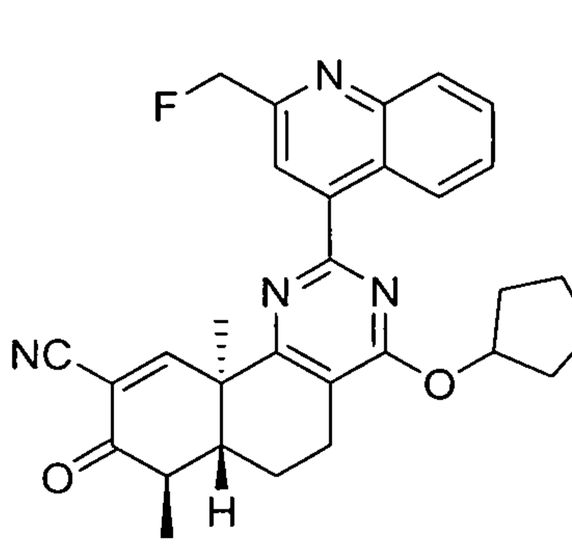
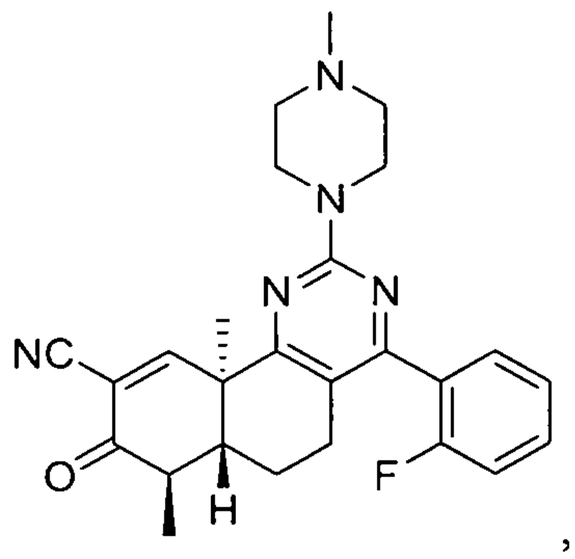
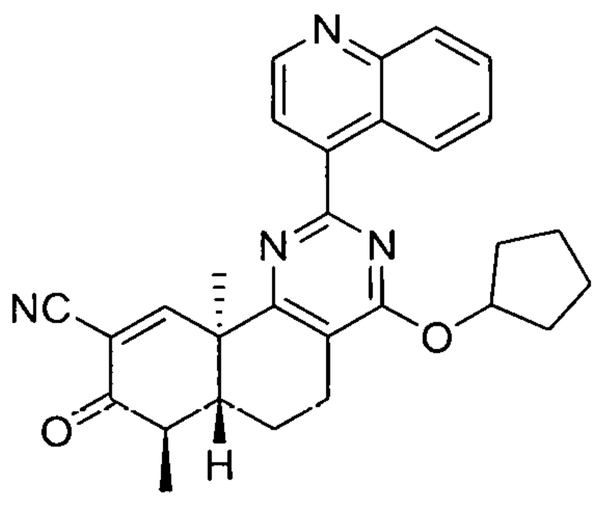
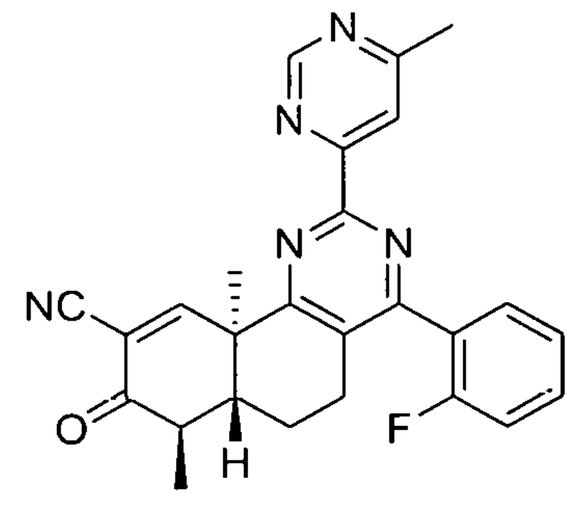
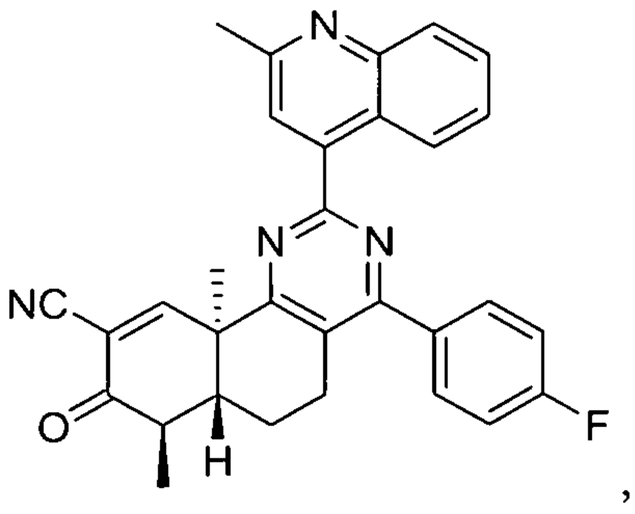
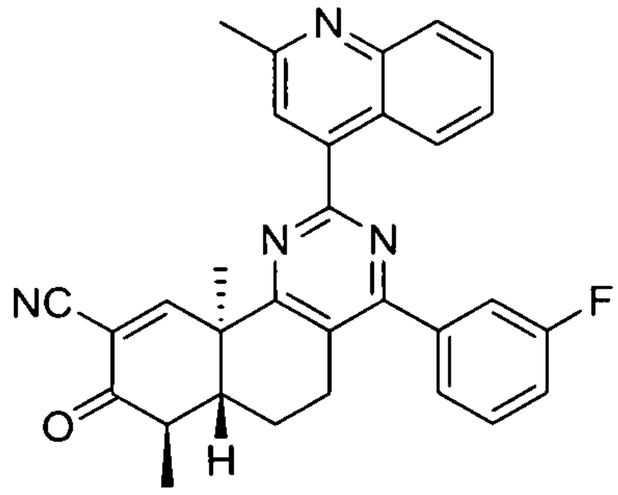
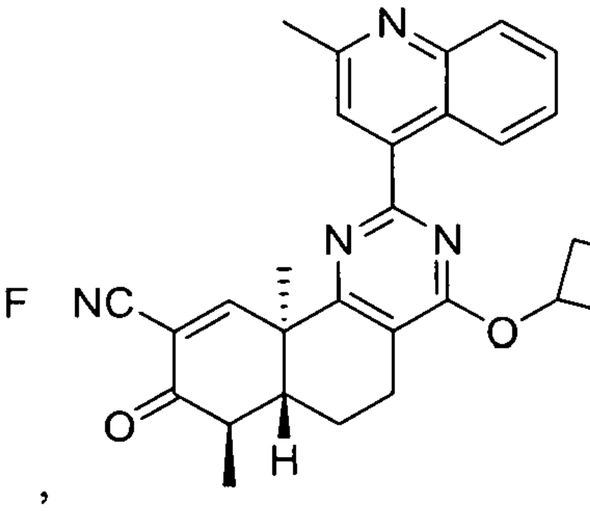
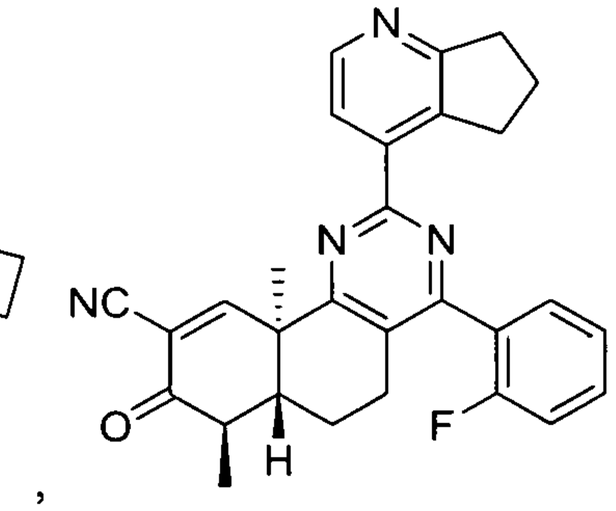

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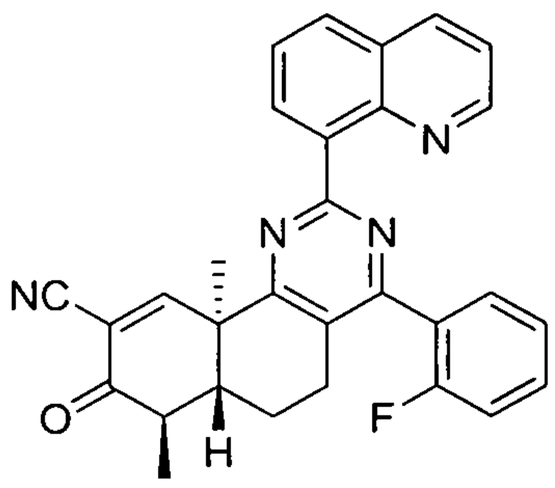
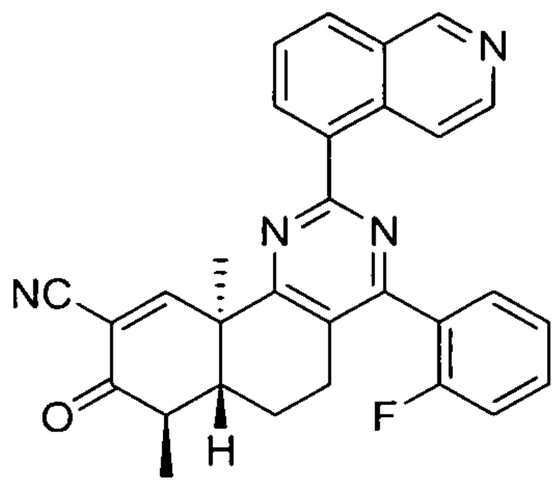
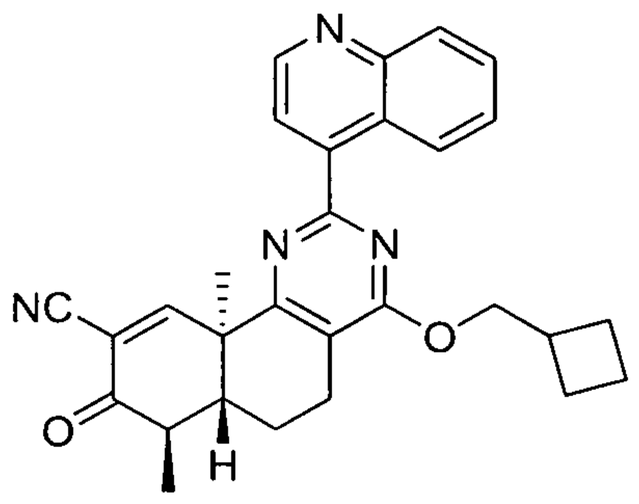
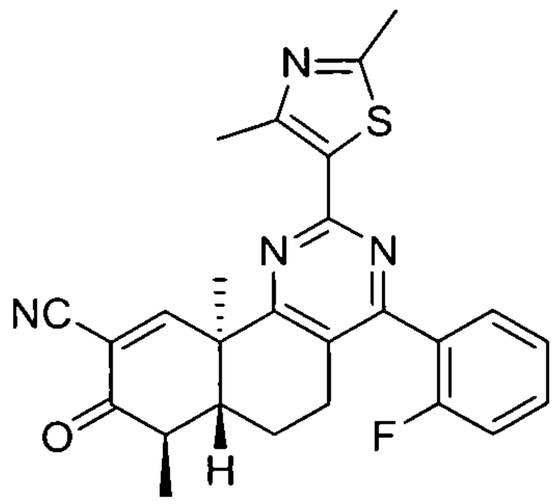
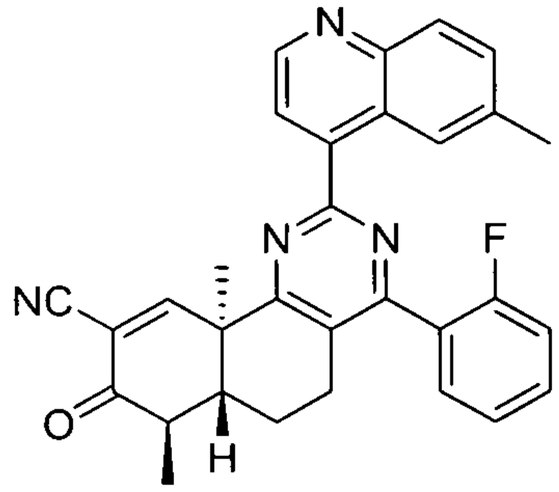
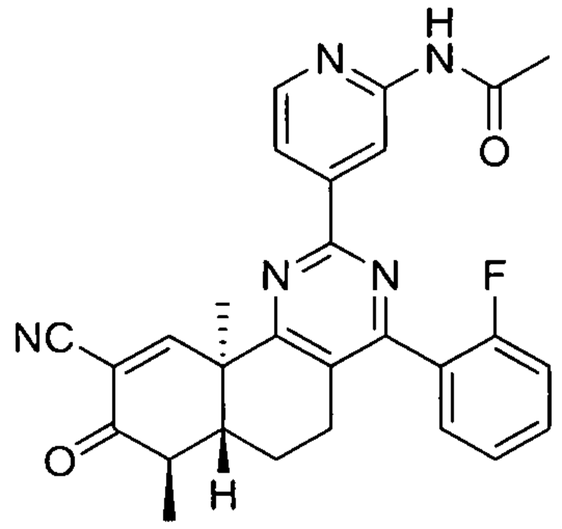
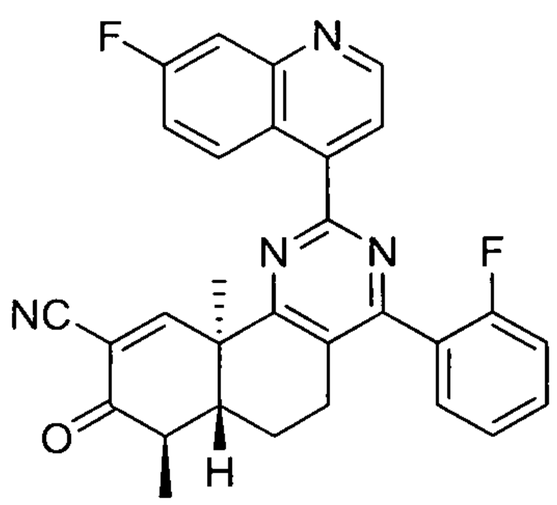
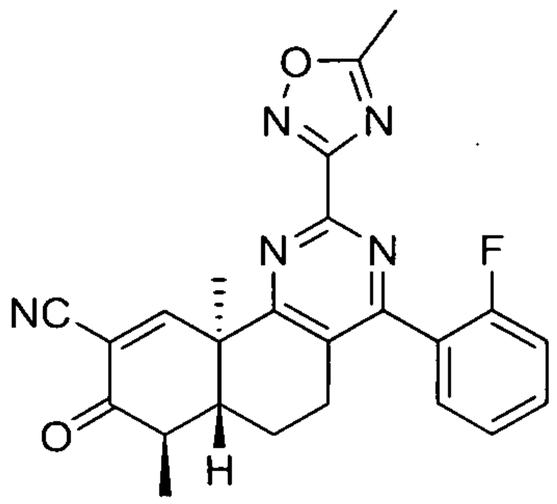
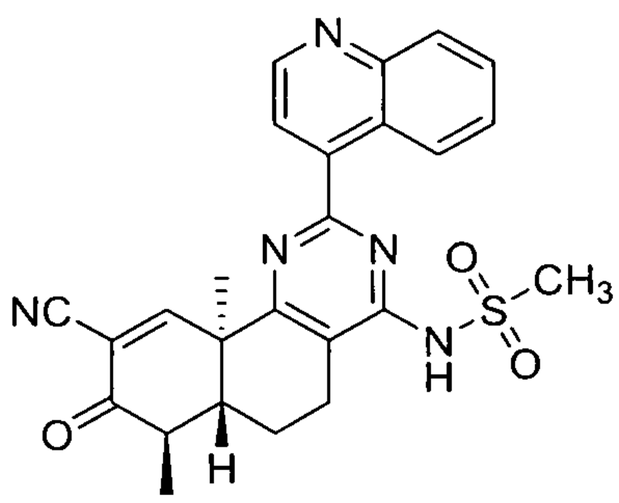
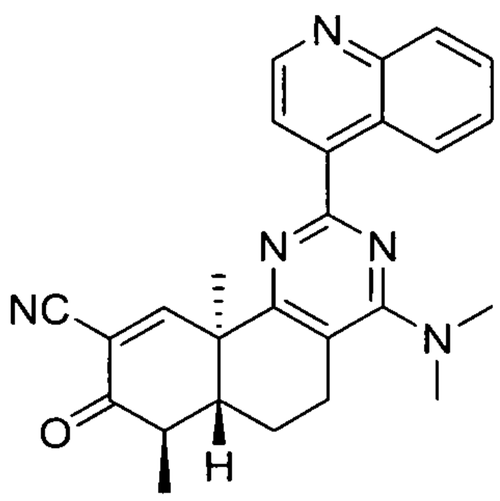
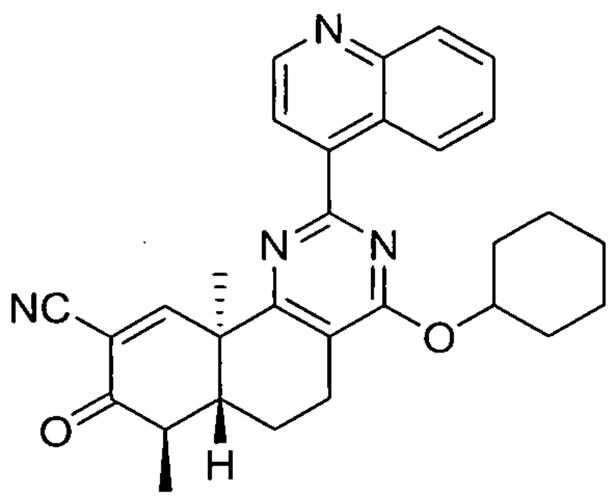
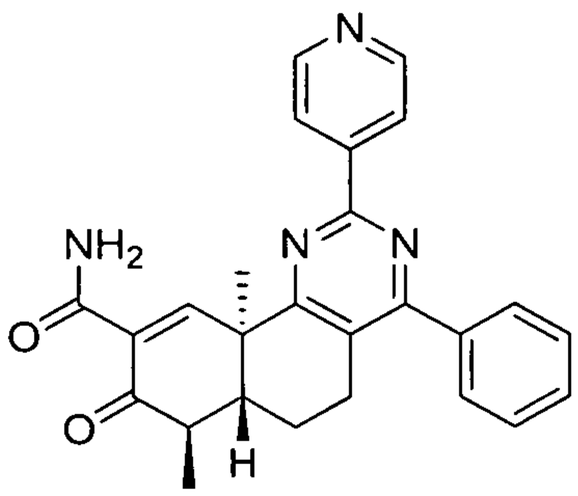
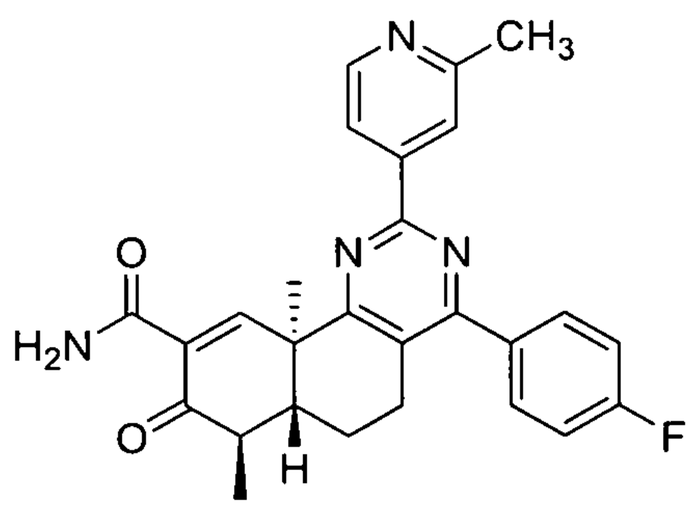
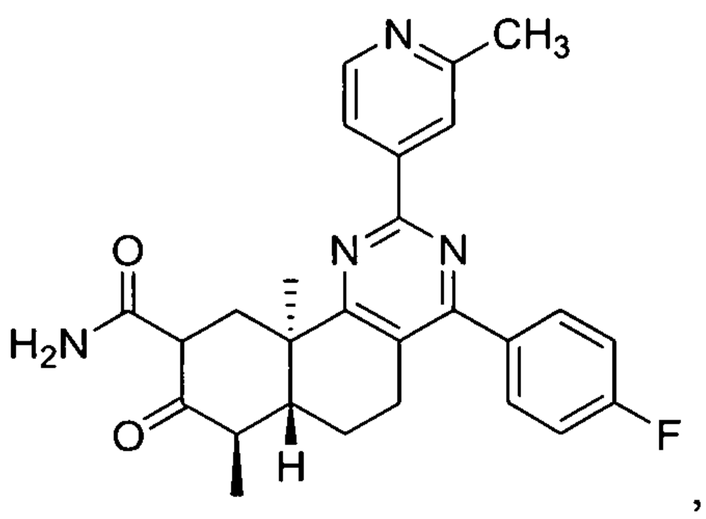

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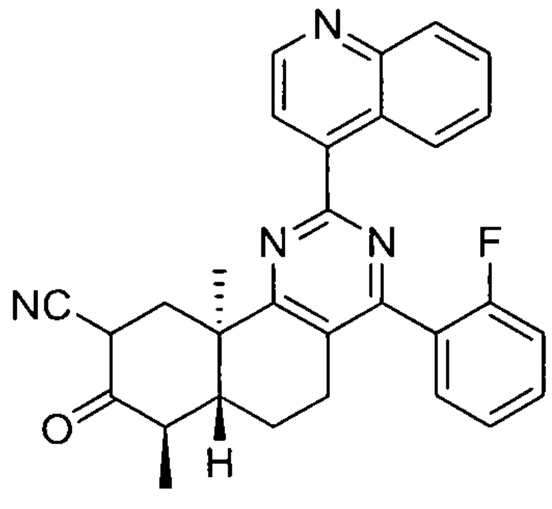
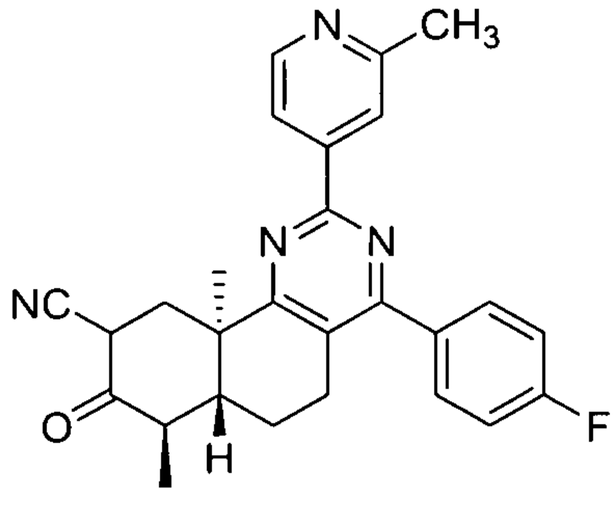
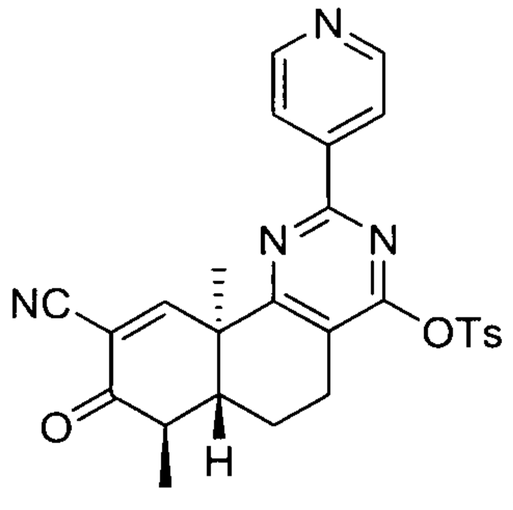
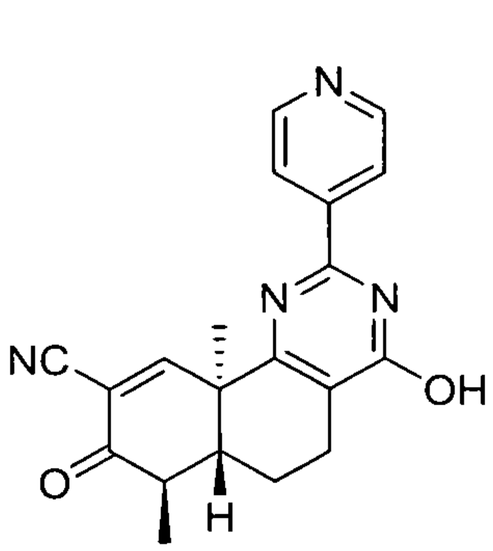
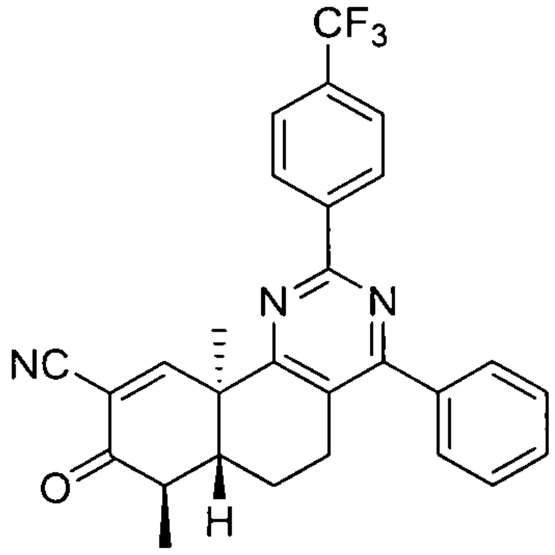
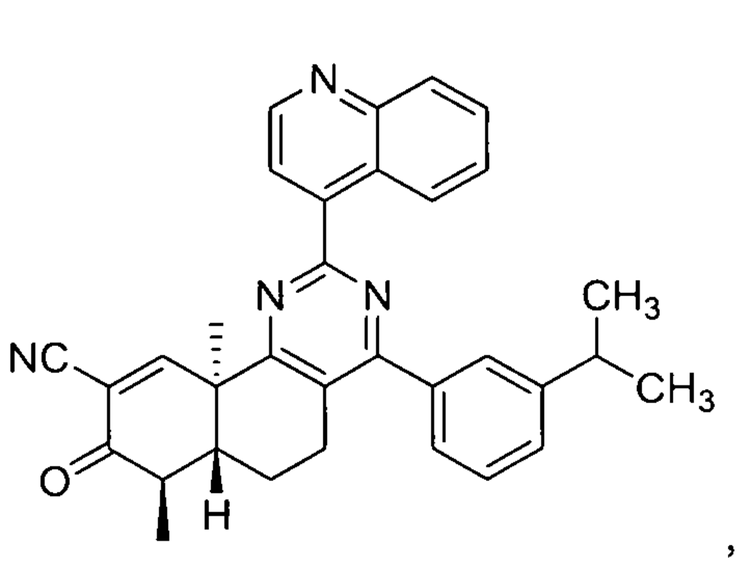
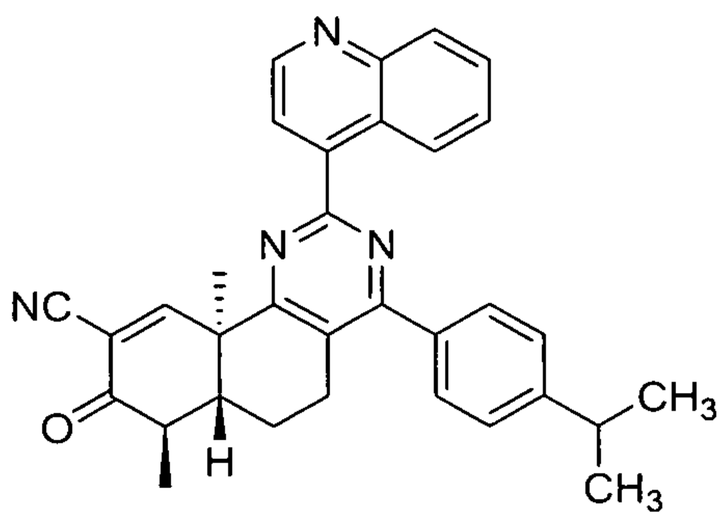
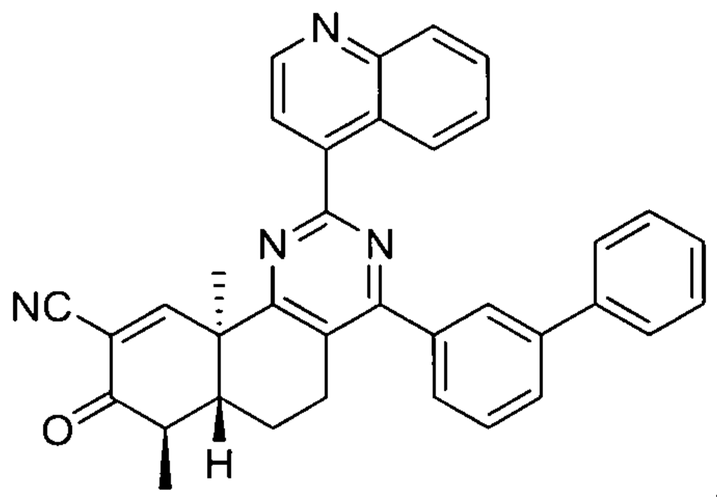
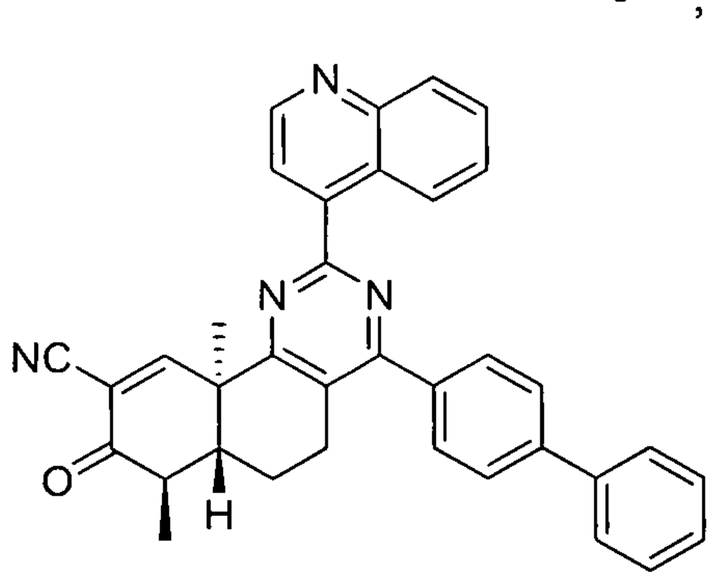
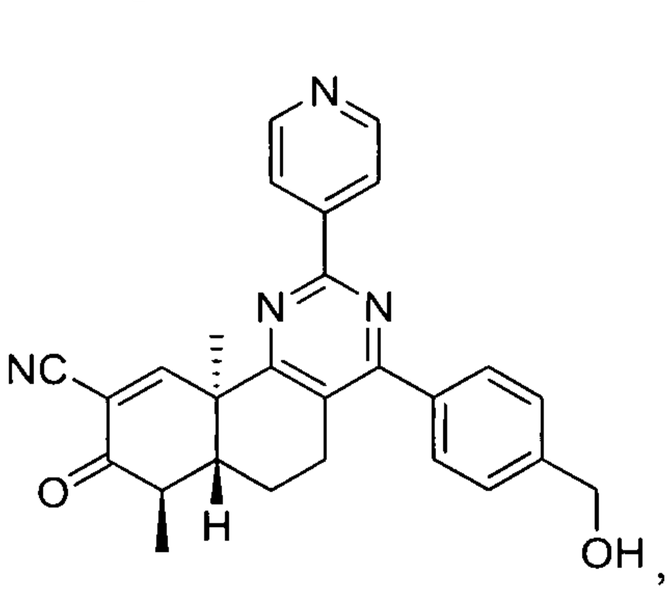
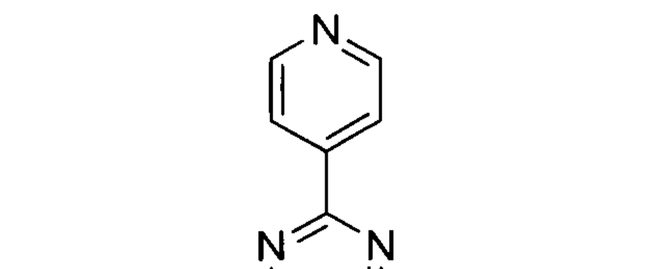
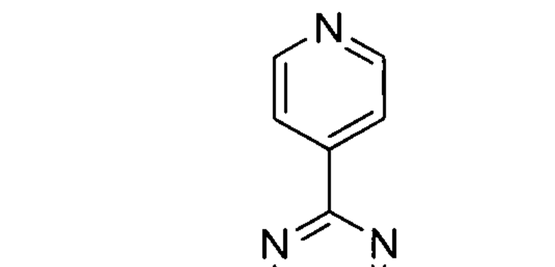
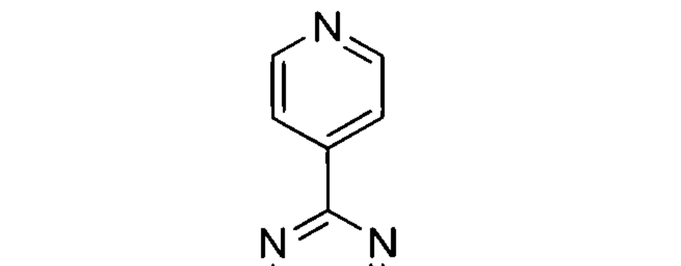

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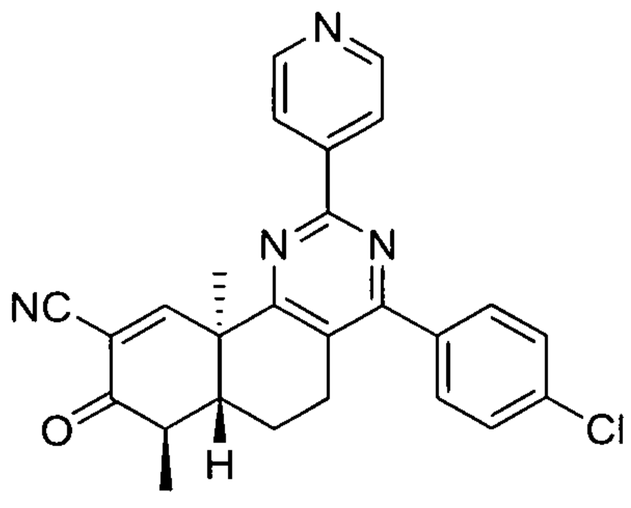
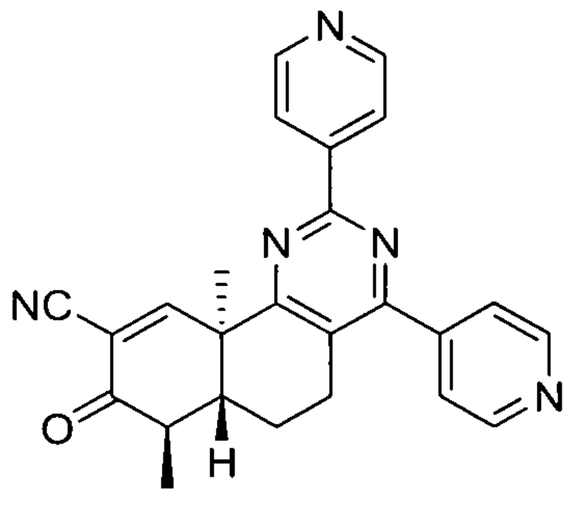
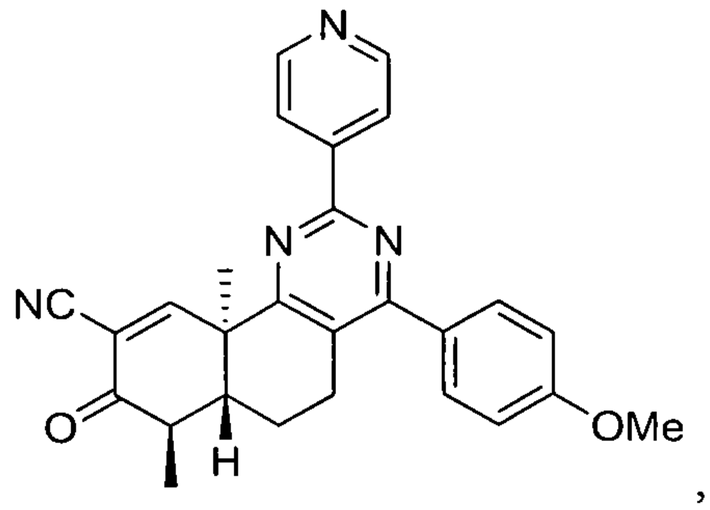
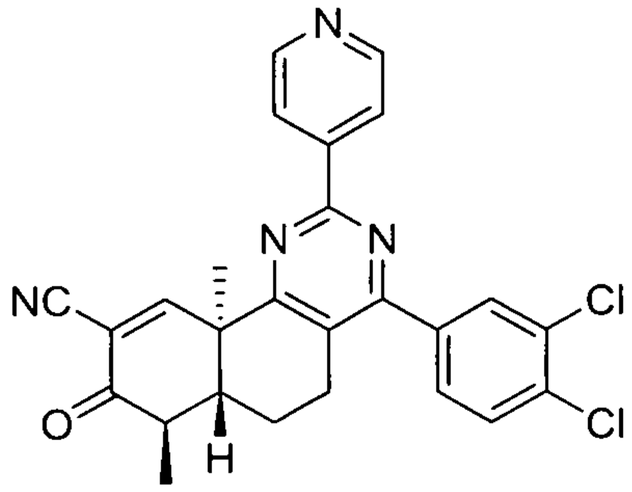
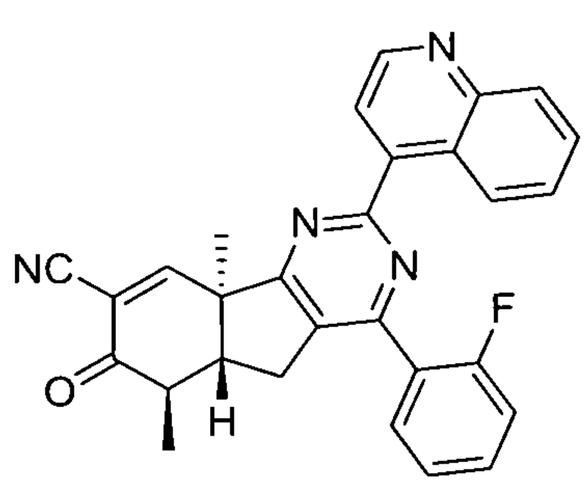
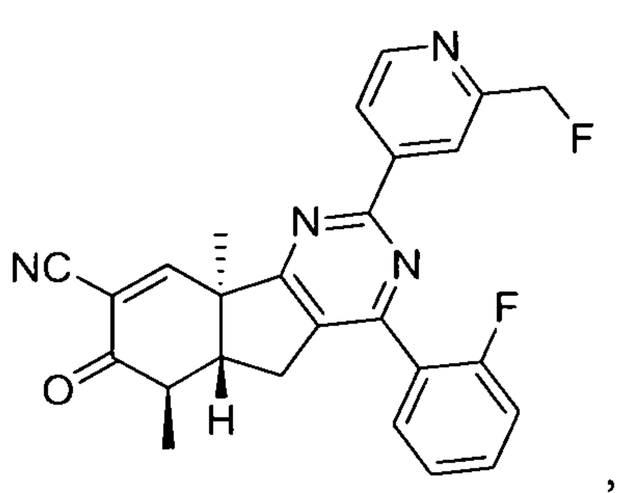
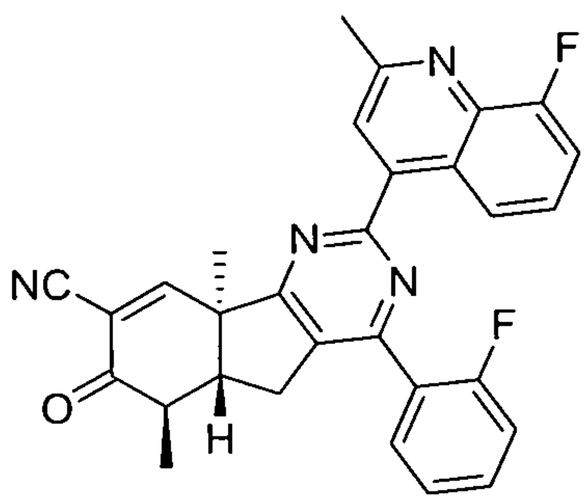
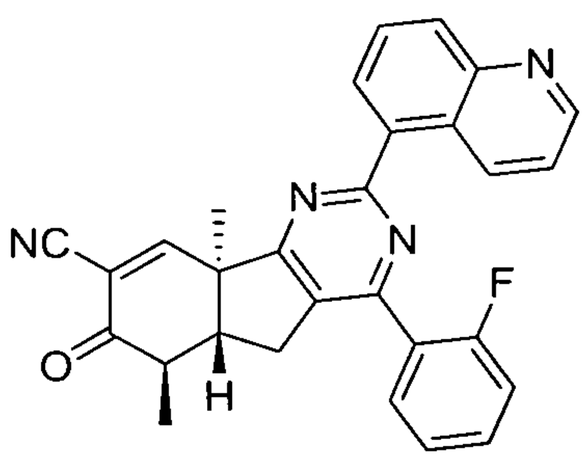
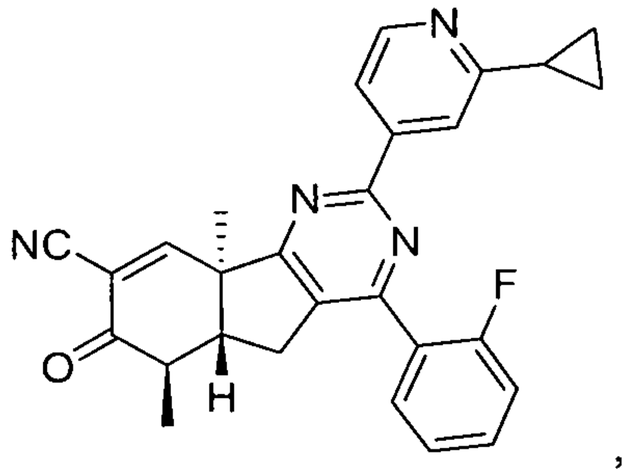
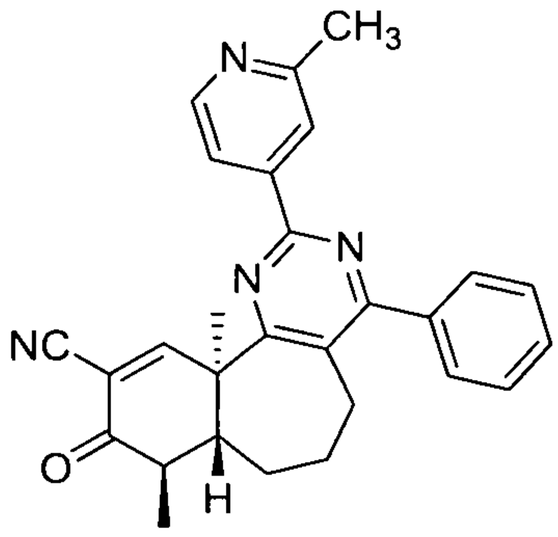
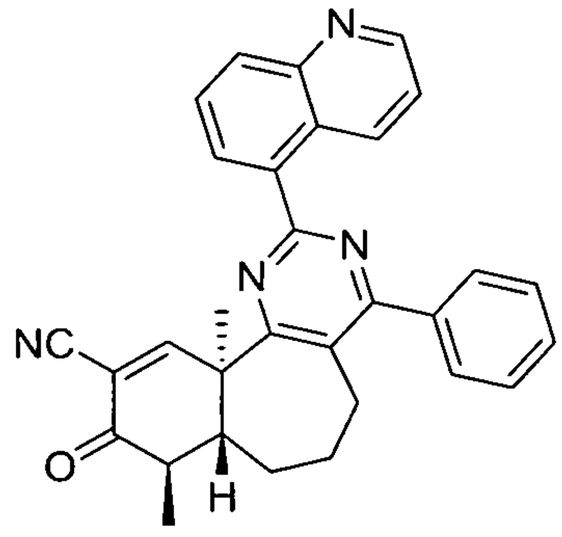
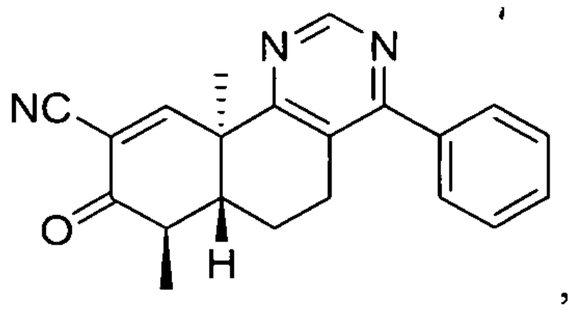
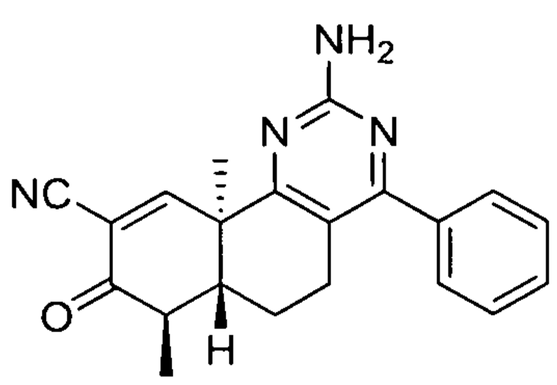
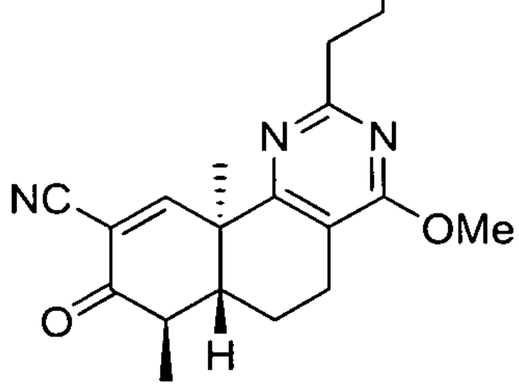
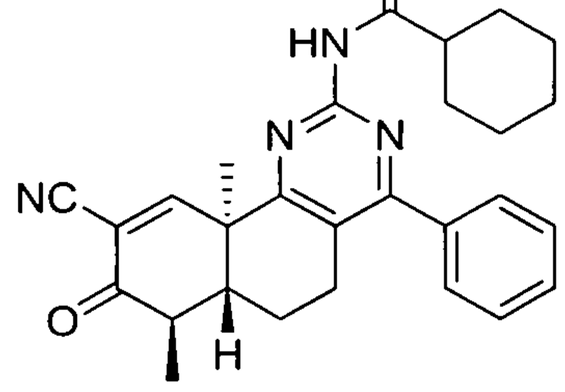

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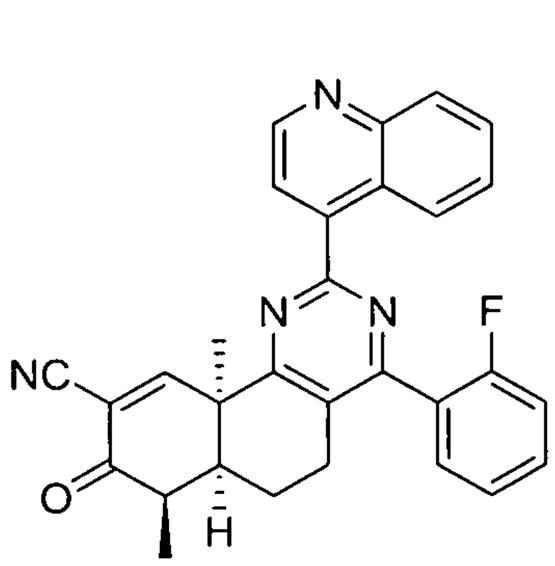
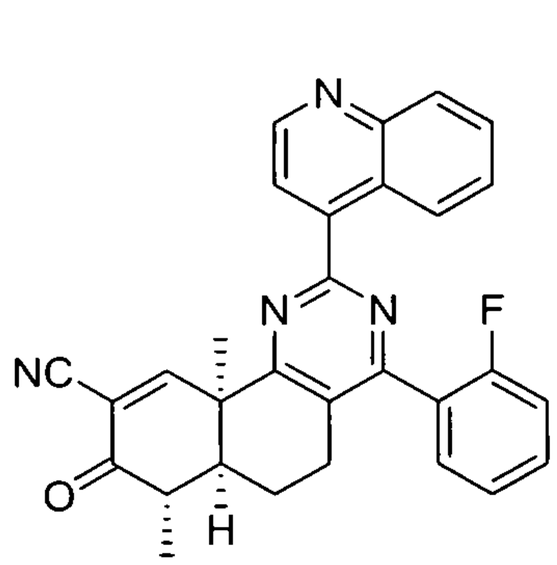
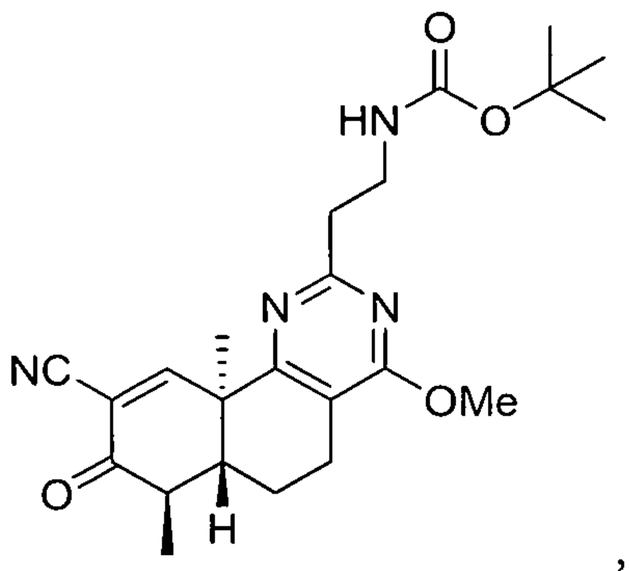
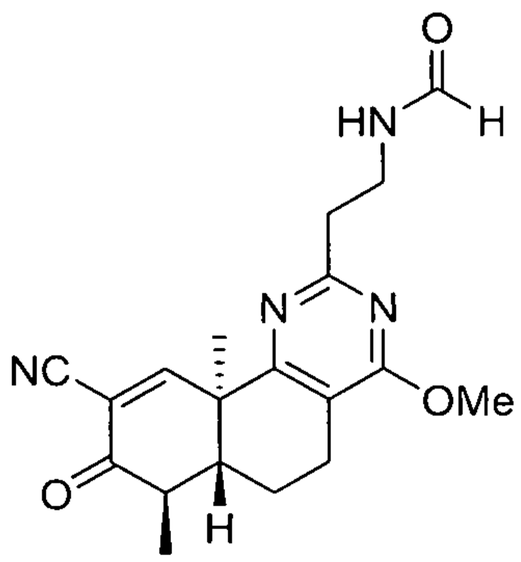
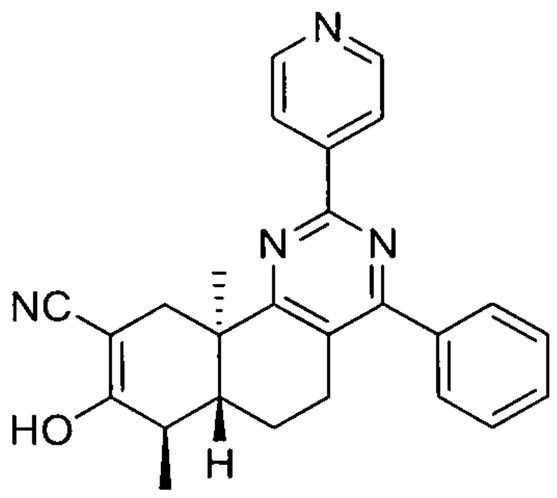
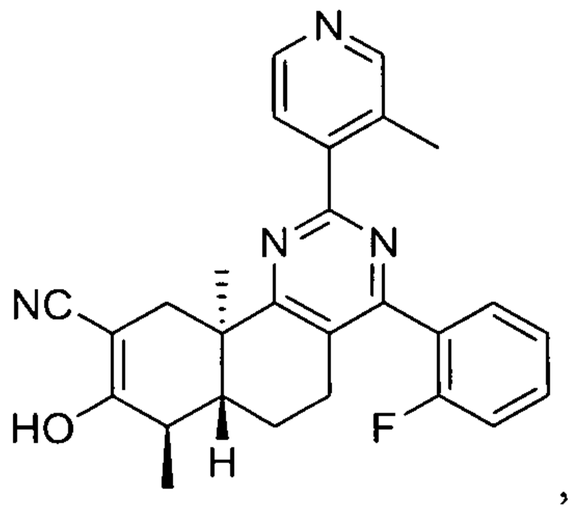
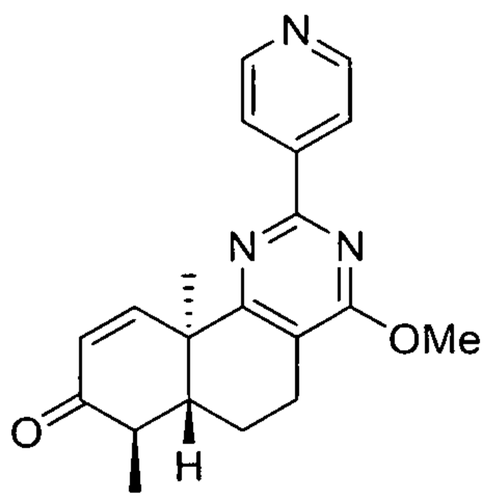
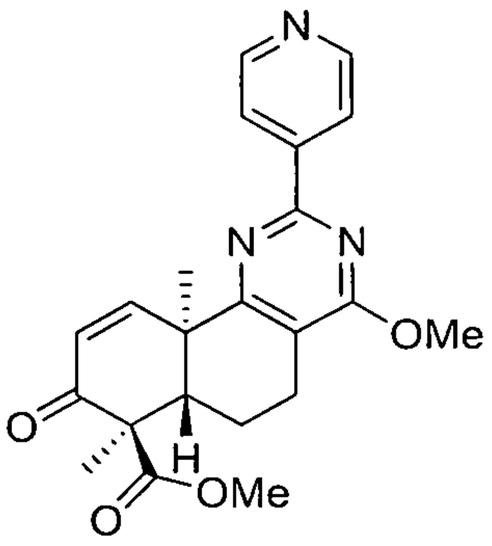

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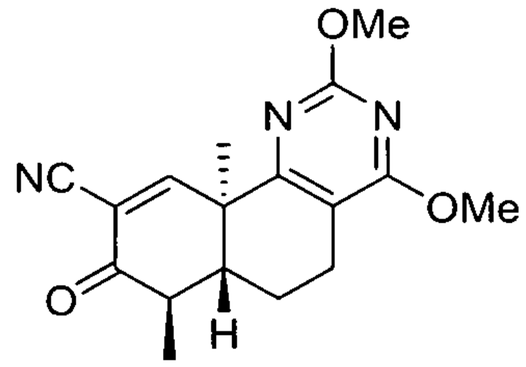
or a pharmaceutically acceptable salt thereof.

149. A compound of the formula:


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, or ;

or a pharmaceutically acceptable salt thereof.

150. A compound of the formula:



or a pharmaceutically acceptable salt thereof.

151. A compound further defined as:

(6a*R*,7*R*,10a*S*)-9-cyano-2,4-dimethoxy-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-2-(2-methoxypyridin-4-yl)-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(3-methylpyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(pyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-2-(2-fluoropyridin-4-yl)-9-cyano-4-methoxy-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(pyridin-3-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(pyridin-4-ylamino)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(6H)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-2-(quinolin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

tert-butyl (2-((6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)ethyl)carbamate;

N-(2-((6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)ethyl)formamide;

(6a*R*,7*R*,10a*S*)-2-(2-aminoethyl)-9-cyano-4-methoxy-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(6H)-one;

(6a*R*,7*R*,10a*R*)-8-hydroxy-7,10a-dimethyl-4-phenyl-2-(pyridin-4-yl)-5,6,6a,7,10,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-7,9b-dimethyl-8-oxo-4-phenyl-2-(pyridin-4-yl)-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carboxamide;

(6a*R*,7*R*,10a*S*)-4-hydroxy-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-4-yl 4-methylbenzenesulfonate;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2,4-diphenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(4-(trifluoromethyl)phenyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-(hydroxymethyl)phenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-cyclohexyl-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-4-(4-(trifluoromethyl)phenyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-(pyridin-3-yl)-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-4-(3-(trifluoromethyl)phenyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-4-(p-tolyl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-chlorophenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*))-7,10a-dimethyl-8-oxo-2,4-di(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-methoxyphenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3,4-dichlorophenyl)-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-phenyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-methoxypyridin-4-yl)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-amino-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)cyclohexanecarboxamide;

(6a*R*,7*R*,10a*S*)-4-benzyl-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(*R*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,8,10a-tetrahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-9-cyano-4-isopropoxy-7,10a-dimethyl-2-(quinolin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-isopropyl-7,10a-dimethyl-2-(quinolin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

tert-butyl 4-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)piperidine-1-carboxylate;

4-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)piperidin-1-ium chloride;

(6a*R*,7*R*,10a*S*)-2-(1-acetylpiperidin-4-yl)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

tert-butyl 5-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)-3,6-dihydropyridine-1(*2H*)-carboxylate;

5-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)-1,2,3,6-tetrahydropyridin-1-ium chloride;

(6a*R*,7*R*,10a*S*)-2-(1-acetyl-1,2,5,6-tetrahydropyridin-3-yl)-7,10a-dimethyl-8-oxo-4-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2,4-difluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(2-(trifluoromethyl)pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*R*)-4-(2-fluorophenyl)-8-hydroxy-7,10a-dimethyl-2-(3-methylpyridin-4-yl)-5,6,6a,7,10,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(3-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(3-fluoropyridin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(5-methylpyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-3-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-6-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)acetamide;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-8-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(8-fluoro-2-methylquinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-morpholinopyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(2-phenylpyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(isoquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(pyrazolo[1,5-a]pyridin-3-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(8-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2,4-dimethylthiazol-5-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(5-methyl-1,2,4-oxadiazol-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(1-methyl-*1H*-pyrrolo[2,3-b]pyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(isoquinolin-1-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(7-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(8-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-methylpyrimidin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(pyridazin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6,7-dihydro-*5H*-cyclopenta[*b*]pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2,4-bis(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(2-(hydroxymethyl)pyridin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(quinolin-5-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6-fluoro-2-methylquinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(isoquinolin-5-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(3,5-dimethylisoxazol-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-methylpyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(6-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6,8-difluoroquinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(4-methylpiperazin-1-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-morpholino-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclopropyl-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclobutoxy-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclobutylmethoxy)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclohexyloxy)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-4-yl)methanesulfonamide;

(6a*R*,7*R*,10a*S*)-4-(dimethylamino)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3,5-dimethylisoxazol-4-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

N-benzyl-4-((6a*R*,7*R*,10a*S*)-9-cyano-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-4-yl)-*N*-methylbenzamide;

(6a*R*,7*R*,10a*S*)-4-(furan-2-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(benzofuran-2-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-4-(5-methylfuran-2-yl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-4-(3-methyl-1,2,4-oxadiazol-5-yl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-4-(thiazol-2-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-fluorophenyl)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclobutoxy-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-7,10a-dimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-cyclobutoxy-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinazolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-(fluoromethyl)quinolin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(2-formylquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)quinolin-2-yl)methyl acetate;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-7,7,10a-trimethyl-2-(2-methylquinolin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-2-(2-(fluoromethyl)quinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(cyclopentyloxy)-2-(8-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-2-(2-(fluoromethyl)quinolin-4-yl)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-2-(2-isopropylquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-7-propyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-7-ethyl-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-2-(8-fluoroquinolin-4-yl)-7,7,10a-trimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(*R*)-4-(2-fluorophenyl)-2-(8-fluoroquinolin-4-yl)-7,10a-dimethyl-8-oxo-5,6,8,10a-tetrahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-2-(7-fluoroquinolin-4-yl)-7,9b-dimethyl-8-oxo-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,9b-dimethyl-8-oxo-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-2-(isoquinolin-4-yl)-7,9b-dimethyl-8-oxo-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-7,9b-dimethyl-8-oxo-2-(quinolin-4-yl)-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*S*,8a*S*,9a*S*,9b*R*)-4-(2-fluorophenyl)-7,7,9b-trimethyl-8-oxo-2-(quinolin-4-yl)-6,6a,7,8,9a,9b-hexahydrooxireno[2',3':3,4]benzo[1,2-*h*]quinazoline-8a(*5H*)-carbonitrile;

(6a*R*,7*R*,10a*R*)-4-methoxy-7,10a-dimethyl-2-(pyridin-4-yl)-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

methyl (6aS,7R,10aR)-4-methoxy-7,10a-dimethyl-8-oxo-2-(pyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-7-carboxylate;

(6a*S*,7*R*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7-(3-hydroxypropyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-7-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7,10a-dimethyl-8-oxo-4-(pyrrolidin-1-yl)-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(4-acetylpiperazin-1-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(6-cyclopropylpyridin-3-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(6-phenylpyridin-3-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(6-(2-(methylsulfonyl)ethyl)pyridin-3-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-((methylsulfonyl)methyl)pyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-2-(2-(2-(methylsulfonyl)ethyl)pyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-7-allyl-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-10a-methyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-10a-methyl-8-oxo-7-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7-methyl-8-oxo-10a-phenyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7-methyl-8-oxo-10a-phenyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-4-(2-fluorophenyl)-7,7,10a-trimethyl-8-oxo-2-(quinolin-5-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)propanoic acid;

ethyl 3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)propanoate;

3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)-*N*,*N*-dimethylpropanamide;

(6a*R*,7*R*,10a*S*)-2-(2-(2-(ethylsulfonyl)ethyl)pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-((ethylsulfonyl)methyl)pyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-8-oxo-10a-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-4-(2-fluorophenyl)-8-oxo-10a-propyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,10a*R*)-7-(cyclopropylmethyl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-10a-methyl-8-oxo-7-propyl-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-10a-methyl-8-oxo-7-propyl-2-(quinolin-5-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(3-isopropylphenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-isopropylphenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-([1,1'-biphenyl]-3-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-([1,1'-biphenyl]-4-yl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-4-(2-fluorophenyl)-10a-isopentyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-10a-isopentyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-4-(2-fluorophenyl)-7,10a-dimethyl-7-(2-methylallyl)-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-8-oxo-10a-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-8-oxo-7,10a-dipropyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7-methyl-8-oxo-10a-propyl-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(5a*R*,6*R*,9a*S*)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-2-(quinolin-4-yl)-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-2-(2-(fluoromethyl)pyridin-4-yl)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-2-(8-fluoro-2-methylquinolin-4-yl)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-2-(quinolin-5-yl)-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(5a*R*,6*R*,9a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(6a*S*,7*S*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)propanamide;

N-(2-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)ethyl)acetamide;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(3-phenylpyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(3-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-7-ethyl-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(7a*R*,8*R*,11a*S*)-8,11a-dimethyl-2-(2-methylpyridin-4-yl)-9-oxo-4-phenyl-6,7,7a,8,9,11a-hexahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-10-carbonitrile;

(7a*R*,8*R*,11a*S*)-8,11a-dimethyl-9-oxo-4-phenyl-2-(quinolin-5-yl)-6,7,7a,8,9,11a-hexahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-10-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carboxamide;

(6a*R*,7*R*,10a*R*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline-9-carboxamide; and

(6a*R*,7*R*,10a*R*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline-9-carbonitrile;

or a pharmaceutically acceptable salt thereof.

152. A pharmaceutical composition comprising:

(A) a compound according to any one of claims 1-151; and

(B) an excipient.

153. The pharmaceutical composition of claim 152, wherein the pharmaceutical composition is formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion.

154. The pharmaceutical composition of claim 153, wherein the pharmaceutical composition is formulated for oral administration.

155. The pharmaceutical composition of claim 153, wherein the pharmaceutical composition is formulated for administration via injection.

156. The pharmaceutical composition of claim 155, wherein the pharmaceutical composition is formulated for intraarterial administration, intramuscular administration, intraperitoneal administration, or intravenous administration.

157. The pharmaceutical composition of claim 153, wherein the pharmaceutical composition is formulated for administration topically.

158. The pharmaceutical composition of claim 157, wherein the pharmaceutical composition is formulated for topical administration to the skin or to the eye.

159. The pharmaceutical composition according to any one of claims 152-158, wherein the pharmaceutical composition is formulated as a unit dose.

160. A method of treating or preventing a disease or disorder in a patient in need thereof comprising administering to the patient a pharmaceutically effective amount of a compound or composition according to any one of claims 1-159.

161. The method of claim 160, wherein the patient is a mammal.

162. The method of claim 161, wherein the patient is a human.

163. The method according to any one of claims 160-162, wherein the disease or disorder is associated with increased production of cytokine IL-17.

164. The method according to any one of claims 160-163, wherein the disease or disorder is associated with dysregulated angiogenesis.

165. The method according to any one of claims 160-164, wherein the disease or disorder is an autoimmune disease, organ rejection, asthma, cancer, a neurological disorder, a psychiatric disorder, a neuropsychiatric disorder, chronic pain syndrome, an inflammatory condition, a retinal disorder, or a cardiovascular disease.

166. The method of claim 165, wherein the disease or disorder is cancer.

167. The method of claim 165, wherein the autoimmune disease is psoriasis, multiple sclerosis, scleroderma, rheumatoid arthritis, lupus, psoriatic arthritis, ankylosing spondylitis, Sjögren syndrome, vitiligo, uveitis, dry eye syndrome, systemic sclerosis, type 1 diabetes, myasthenia gravis, and inflammatory bowel disease.

168. The method of claim 165, wherein the cardiovascular disease is vasculitis, atherosclerosis, myocardial infarction, myocarditis, heart failure, pulmonary hypertension, or stroke.

169. The method of claim 165, wherein the neurological disorder is epilepsy, multiple sclerosis, spinal cord injury, Guillain-Barre syndrome, or another neurological disorder involving dysregulated inflammatory signaling or oxidative stress.

170. The method of claim 169, wherein the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease.

171. The method of claim 165, wherein the inflammatory condition is pancreatitis, hepatitis, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, dermatitis, gastritis, esophagitis, irritable bowel syndrome, inflammatory bowel disease, nephritis, muscle wasting, or osteoarthritis.

172. The method of claim 165, wherein the chronic pain syndrome is fibromyalgia or neuropathic pain.

173. The method of claim 165, wherein the disease or disorder is a severe inflammatory response to a pathogen.

174. The method of claim 173, wherein the severe inflammatory response to a pathogen is from encephalitis, meningitis, *H. pylori*, *Toxoplasma gondii*, or *Leishmania spp.*

175. The method of claim 165, wherein the disease or disorder is obesity or a condition associated with obesity.

176. The method of claim 175, wherein the condition associated with obesity is insulin resistance or fatty liver disease.

177. The method of claim 165, wherein the retinal disorder is macular degeneration or another disorder of the retina.

178. The method of claim 160, wherein the disease or disorder is associated with inflammation.

179. The method of claim 178, wherein the disease or disorder associated with inflammation is obesity, Type 2 diabetes, or a complication of Type 1 or Type 2 diabetes.

180. The method of claim 179, wherein the complication of Type 1 or Type 2 diabetes is neuropathy, reduced kidney function or chronic kidney disease, retinopathy, diabetic ulcers, or cardiovascular disease.

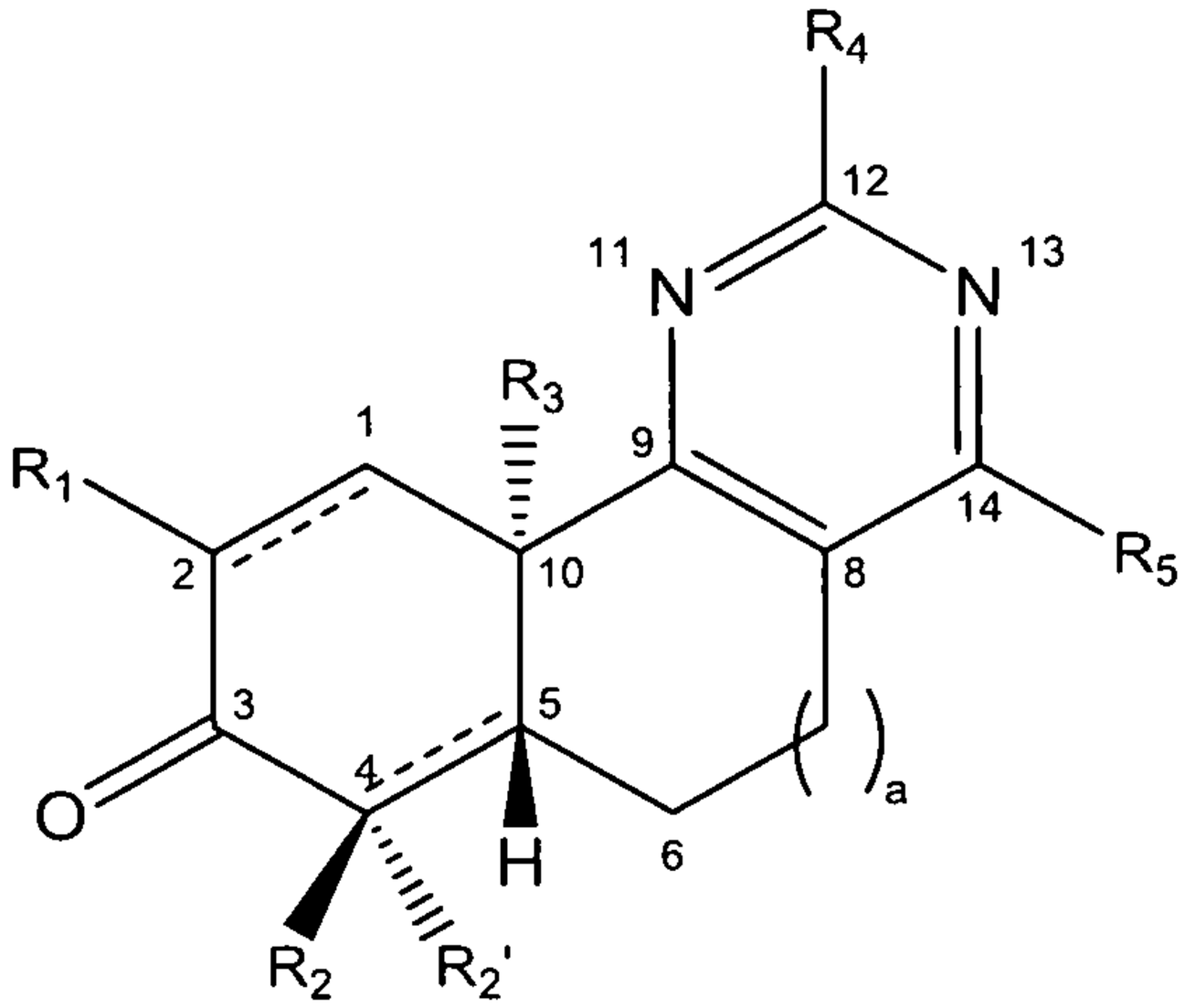
181. The method of claim 178, wherein the disease or disorder associated with inflammation is chronic kidney disease.

182. The method of claim 181, wherein the chronic kidney disease is hereditary.

183. The method of claim 181, wherein the chronic kidney disease is due to a non-hereditary cause.

184. The method according to any one of claims 160-174, wherein the method comprises administering the compound once.

185. The method according to any one of claims 160-174, wherein the method comprises administering the compound two or more times.



(I)