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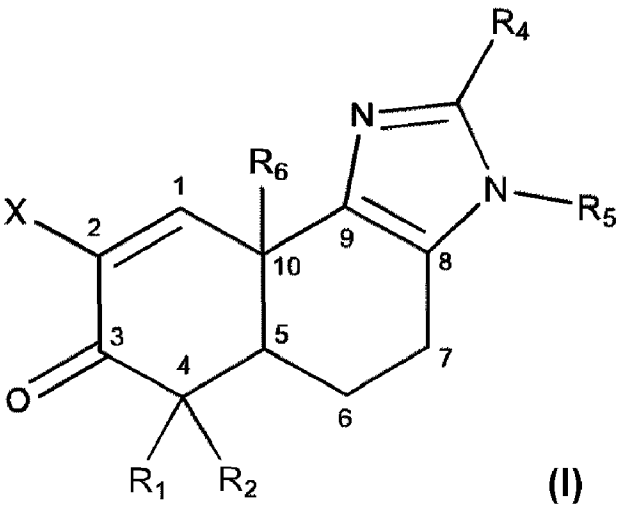
(54) Titre : ENONES TRICYCLIQUES D'IMIDAZOLYLE COMME MODULATEURS ANTIOXYDANTS DE L'INFLAMMATION

(54) Title: IMIDAZOLYL TRICYCLIC ENONES AS ANTIOXIDANT INFLAMMATION MODULATORS



(I)

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

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(57) Abrégé(suite)/Abstract(continued):
inflammation modulators. In some aspects, the present disclosure provides methods wherein the compounds and composition described herein are used for the treatment of diseases and disorders associated with inflammation and cancer.

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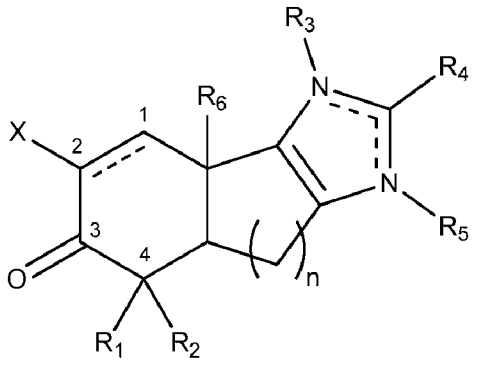
(54) Title: IMIDAZOLYL TRICYCLIC ENONES AS ANTIOXIDANT IFLAMMATION MODULATORS



(I),

(57) Abstract: Disclosed herein are compounds of the formula: (I), wherein the variables are defined herein. Also provided are pharmaceutical compositions thereof. In some aspects, the compounds and compositions provided herein may be used as antioxidant inflammation modulators. In some aspects, the present disclosure provides methods wherein the compounds and composition described herein are used for the treatment of diseases and disorders associated with inflammation and cancer.

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DESCRIPTION

IMIDAZOLYL TRICYCLIC ENONES AS ANTIOXIDANT INFLAMMATION MODULATORS

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 oxidative stress and inflammation.

II. Description of Related Art

The anti-inflammatory and anti-proliferative activity of the naturally occurring triterpenoid, oleanolic acid, has been improved by chemical modifications. For example, 2-cyano-3,12-diooxooleana-1,9(11)-dien-28-oic acid (CDDO) and related compounds have been developed (Honda *et al.,* 1997; Honda *et al.,* 1998; Honda *et al.,* 1999; Honda *et al.,* 2000a; Honda *et al.,* 2000b; Honda, *et al.,* 2002; Suh *et al.* 1998; Suh *et al.,* 1999; Place *et al.,* 2003; Liby *et al.,* 2005). Compounds derived from oleanolic acid have also been shown to affect the function of multiple protein targets and thereby modulate the activity of several important cellular signaling pathways related to oxidative stress, cell cycle control, and inflammation. See, for example, Dinkova-Kostova *et al.*, 2005; Ahmad *et al.*, 2006; Ahmad *et al.*, 2008; Liby *et al.*, 2007a and U.S. Patents 8,129,429, 7,915,402, 8,124,799, 7,943,778 and WO 2013/163344. The methyl ester, bardoxolone-methyl (CDDO-Me), has been evaluated as a treatment for diabetic nephropathy, chronic kidney disease, and cancer (Pergola, *et al.*, 2011; Hong, *et al.*, 2012). Bardoxolone methyl is currently being evaluated for the treatment of pulmonary arterial hypertension (WO 2015/027206). Other analogs of CDDO have been developed and evaluated for other indications for treatment of diseases or disorders which are associated with inflammation or cellular proliferation (WO 2013/163344 and Reisman, *et al.*, 2014).

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Despite these promising properties, oleanolic acid derivatives are all dependent on natural product precursors. Use of other, including simpler or less expensive starting materials can minimize supply chain-related risks, including potential lack of availability due to adverse weather conditions, disease, and other environmental factors. Previous synthetic efforts include a class of compounds known as tricyclic bis-enones (TBEs) (Honda, *et al.*, 2003; Favaloro, *et al.*, 2002; WO 2008/064133; Honda, *et al.*, 2011). These TBE compounds contained two cyano enone structures, one in each of the A and C rings. More recently, tricyclic compounds with pyrazolyl or pyrimidinyl groups were developed (WO 2012/083306). The further development of new compounds continues to be of interest because the biological activity profiles of known antioxidant inflammation modulating compounds varies and because of the wide variety of potential diseases and disorders that may be treated or prevented with such compounds, as well as manufacturing and supply-chain related considerations.

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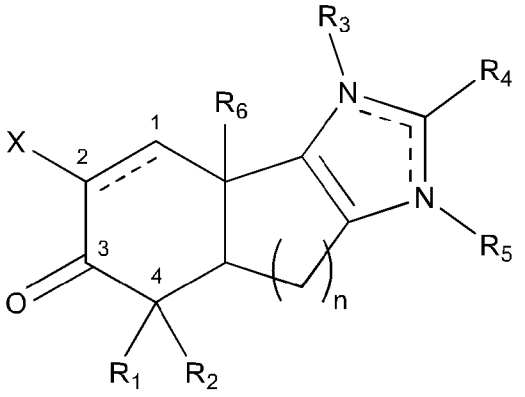
SUMMARY OF THE INVENTION

The present disclosure provides novel compounds, including imidazolyl tricyclic enones with anti-inflammatory and/or antioxidant properties, pharmaceutical compositions thereof, methods for their manufacture, and methods for their use.

In one aspect of the present disclosure there are provided compounds of the formula:



(I),

wherein: the atoms labeled 1 and 2 are connected either by a single bond, a double bond or an epoxidized double bond; n is 1 or 2; X is −CN, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $-NH_2$, $alkoxy_{(C\leq 6)}$, $alkylamino_{(C\leq 6)}$, $dialkylamino_{(C\leq 6)}$, or $-NHS(O)_2-alkyl_{(C1-4)}$; R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $arylamino_{(C\leq 12)}$, $aralkylamino_{(C\leq 12)}$, $heteroarylamino_{(C\leq 12)}$, $amido_{(C\leq 12)}$, or a substituted version of any of these groups; or R_1 and R_2 are taken together and are $alkanediyl_{(C\leq 12)}$, $alkenediyl_{(C\leq 12)}$, $alkoxydiyl_{(C\leq 12)}$, $alkylaminodiyl_{(C\leq 12)}$, or a substituted version of any of these groups; R_3 is: absent, hydrogen; or $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$ or a substituted version of any of these groups, provided that R_3 is absent when the atom to which it is bound forms part of a double bond; R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $arylamino_{(C\leq 12)}$,

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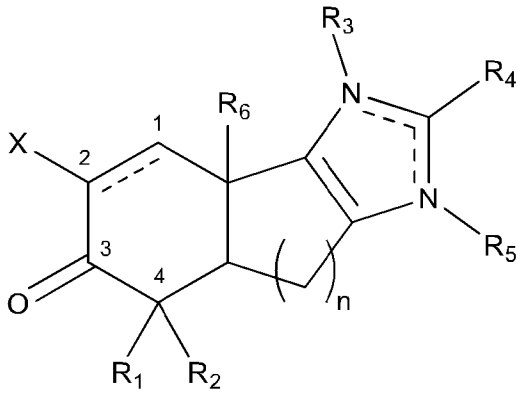
aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or −alkanediyl$_{(C\leq6)}$−Y_1, wherein Y_1 is: hydroxy, amino, halo, or cyano; or acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of these groups; and R_5 is: absent, hydrogen, hydroxy, or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; provided that R_5 is absent when the atom to which it is bound forms part of a double bond; −alkanediyl$_{(C\leq6)}$−Y_2; −arenediyl$_{(C\leq8)}$−Y_3; or −arenediyl$_{(C\leq8)}$−alkanediyl$_{(C\leq6)}$−Y_4, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; R_6 is alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is further defined by the formula:



(I),

wherein: the atoms labeled 1 and 2 are connected either by a single bond, a double bond or an epoxidized double bond; n is 1 or 2; X is −CN, −CF_3, or −C(O)R_a, wherein R_a is −OH, −NH_2, alkoxy$_{(C\leq6)}$, alkylamino$_{(C\leq6)}$, dialkylamino$_{(C\leq6)}$, or −NHS(O)$_2$−alkyl$_{(C1\text{-}4)}$; R_1 and R_2 are each independently hydrogen, hydroxy, halo, or

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amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or R_1 and R_2 are taken together and are $alkanediyl_{(C\leq12)}$, $alkenediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups; R_3 is: absent, hydrogen; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups, provided that R_3 is absent when the atom to which it is bound forms part of a double bond; R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or $-alkanediyl_{(C\leq6)}-Y_1$ wherein Y_1 is: hydroxy, amino, halo, or cyano; or $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of these groups; and R_5 is: absent, hydrogen, hydroxy, or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; provided that R_5 is absent when the atom to which it is bound forms part of a double bond; $-alkanediyl_{(C\leq6)}-Y_2$; $-arenediyl_{(C\leq8)}-Y_3$; or $-arenediyl_{(C\leq8)}-alkanediyl_{(C\leq6)}-Y_4$, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; R_6 is $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt thereof.

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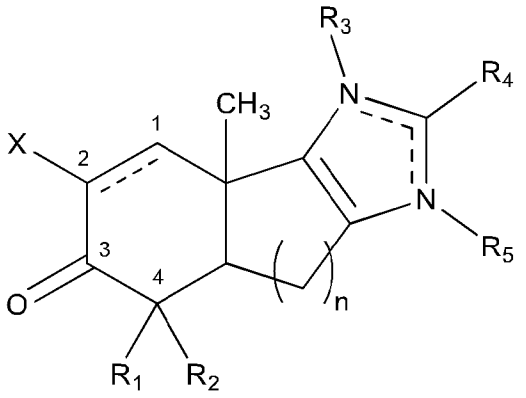
In some embodiments, the compound is further defined by the formula:



(II),

wherein: the atoms labeled 1 and 2 are connected either by a single bond, a double bond or an epoxidized double bond; n is 1 or 2; X is $-CN$, $-CF_3$, or $-C(O)R_a$, wherein R_a is $-OH$, $-NH_2$, $alkoxy_{(C\leq6)}$, $alkylamino_{(C\leq6)}$, $dialkylamino_{(C\leq6)}$, or $-NHS(O)_2-alkyl_{(C1\text{-}4)}$; R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or R_1 and R_2 are taken together and are $alkanediyl_{(C\leq12)}$, $alkenediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups; R_3 is: absent, hydrogen; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups, provided that R_3 is absent when the atom to which it is bound forms part of a double bond; R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or $-alkanediyl_{(C\leq6)}-Y_1$ wherein Y_1 is: hydroxy, amino, halo, or cyano; or $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of these groups; and R_5 is:

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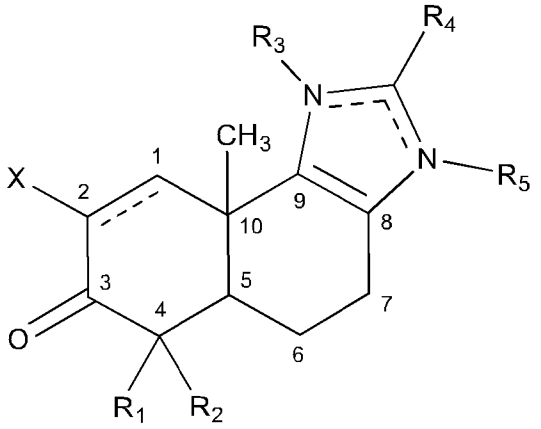
absent, hydrogen, hydroxy, or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; provided that R_5 is absent when the atom to which it is bound forms part of a double bond; –alkanediyl$_{(C\leq6)}$–Y_2; –arenediyl$_{(C\leq8)}$–Y_3; or –arenediyl$_{(C\leq8)}$–alkanediyl$_{(C\leq6)}$–Y_4, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is further defined by the formula:



(III),

wherein: X is –CN, –CF_3, or –C(O)R_a, wherein R_a is –OH, –NH_2, alkoxy$_{(C\leq6)}$, alkylamino$_{(C\leq6)}$, dialkylamino$_{(C\leq6)}$, or –$NHS(O)_2$–alkyl$_{(C1\text{-}4)}$; R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or R_1 and R_2 are taken together and are alkanediyl$_{(C\leq12)}$, alkenediyl$_{(C\leq12)}$, alkoxydiyl$_{(C\leq12)}$, alkylaminodiyl$_{(C\leq12)}$, or a substituted version of any of these groups; R_3 is: absent, hydrogen; or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$,

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aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$ or a substituted version of any of these groups, provided that R_3 is absent when the atom to which it is bound forms part of a double bond; R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or $-$alkanediyl$_{(C\leq6)}-Y_1$ wherein Y_1 is: hydroxy, amino, halo, or cyano; or acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of these groups; and R_5 is: absent, hydrogen, hydroxy, or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; provided that R_5 is absent when the atom to which it is bound forms part of a double bond; –alkanediyl$_{(C\leq6)}-Y_2$; $-$arenediyl$_{(C\leq8)}-Y_3$; or $-$arenediyl$_{(C\leq8)}-$alkanediyl$_{(C\leq6)}-Y_4$, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroaryl-amino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt thereof.

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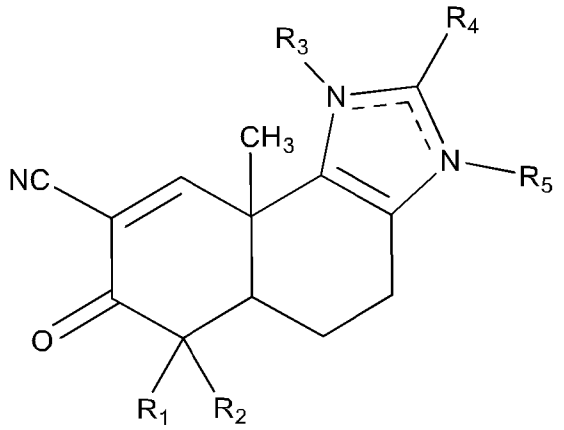
In some embodiments, the compound is further defined by the formula:



(IV),

wherein: R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or R_1 and R_2 are taken together and are $alkanediyl_{(C\leq12)}$, $alkenediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups; R_3 is: absent, hydrogen; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups, provided that R_3 is absent when the atom to which it is bound forms part of a double bond; R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or $-alkanediyl_{(C\leq6)}-Y_1$ wherein Y_1 is: hydroxy, amino, halo, or cyano; or $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of these groups; and R_5 is: absent, hydrogen, hydroxy, or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$,

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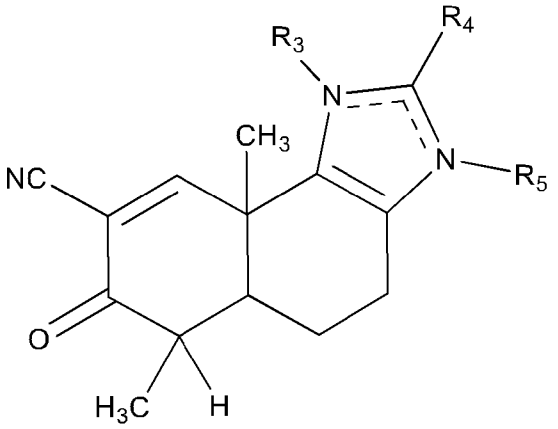
heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; provided that R_5 is absent when the atom to which it is bound forms part of a double bond; –alkanediyl$_{(C\leq6)}$–Y_2; –arenediyl$_{(C\leq8)}$–Y_3; or –arenediyl$_{(C\leq8)}$–alkanediyl$_{(C\leq6)}$–Y_4, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroaryl-amino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is further defined by the formula:



(V),

wherein: R_3 is: absent, hydrogen; or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$ or a substituted version of any of these groups, provided that R_3 is absent when the atom to which it is bound forms part of a double bond; R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or –alkanediyl$_{(C\leq6)}$–Y_1 wherein Y_1 is: hydroxy, amino, halo, or cyano; or acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of these groups; and R_5 is: absent, hydrogen, hydroxy, or alkyl$_{(C\leq12)}$,

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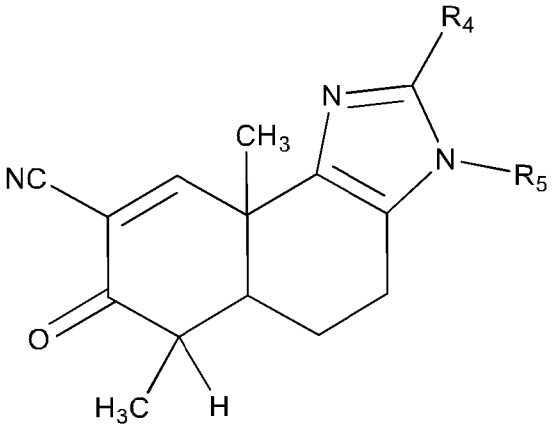
cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; provided that R_5 is absent when the atom to which it is bound forms part of a double bond; –alkanediyl$_{(C\leq6)}$–Y_2; –arenediyl$_{(C\leq8)}$–Y_3; or –arenediyl$_{(C\leq8)}$–alkanediyl$_{(C\leq6)}$–Y_4, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroaryl-amino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is further defined by the formula:



(VI)

wherein: R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or –alkanediyl$_{(C\leq6)}$–Y_1 wherein Y_1 is: hydroxy, amino, halo, or cyano; or acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of these groups; and R_5 is: absent, hydrogen, hydroxy, or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$,

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$aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; provided that R_5 is absent when the atom to which it is bound forms part of a double bond; $-alkanediyl_{(C\leq6)}-Y_2$; $-arenediyl_{(C\leq8)}-Y_3$; or $-arenediyl_{(C\leq8)}-alkanediyl_{(C\leq6)}-Y_4$, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is further defined as: R_4 is: hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; and R_5 is: hydrogen, hydroxy, or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups. In some embodiments, the compound is further defined as: R_4 is hydroxy, amino, halo, cyano, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, or $amido_{(C\leq12)}$; and R_5 is hydrogen, hydroxy, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, or $amido_{(C\leq12)}$.

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In some embodiments, the atoms labeled 1 and 2 are connected by a single bond. In other embodiments, the atoms labeled 1 and 2 are connected by a double bond. In some embodiments, n is 1. In other embodiments, n is 2. In some embodiments, X is cyano. In other embodiments, X is $-C(O)R_a$, wherein R_a is $-OH$, $-NH_2$, $alkoxy_{(C\leq6)}$, $alkylamino_{(C\leq6)}$, $dialkylamino_{(C\leq6)}$, or $-NHS(O)_2-alkyl_{(C1-4)}$. In some embodiments, R_a is $-NH_2$.

In some embodiments, R_1 is hydrogen. In other embodiments, R_1 is $alkyl_{(C\leq12)}$. In some embodiments, R_1 is methyl. In some embodiments, R_2 is hydrogen. In other embodiments, R_2 is $alkyl_{(C\leq12)}$. In some embodiments, R_2 is methyl. In some embodiments, R_3 is absent. In some embodiments, R_3 is absent, hydrogen; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups, provided that R_3 is absent when the atom to which it is bound forms part of a double bond.

In some embodiments, R_4 is hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or $-alkanediyl_{(C\leq6)}-Y_1$, wherein Y_1 is: hydroxy, amino, halo, or cyano; or $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of these groups. In some embodiments, R_4 is cyano. In other embodiments, R_4 is halo. In some embodiments, R_4 is bromo. In other embodiments, R_4 is substituted $acyl_{(C\leq12)}$. In some embodiments, R_4 is $-C(O)NH_2$. In other embodiments, R_4 is $alkyl_{(C\leq12)}$. In some embodiments, R_4 is methyl. In other embodiments, R_4 is substituted $alkyl_{(C\leq12)}$. In some embodiments, R_4 is 2-hydroxyethyl. In other embodiments, R_4 is $aryl_{(C\leq12)}$. In some embodiments, R_4 is phenyl or 2-methylphenyl. In other embodiments, R_4 is $heteroaryl_{(C\leq12)}$. In some embodiments, R_4 is 4-pyridyl or 4-(1-methyl)pyrazolyl. In other embodiments, R_4 is $-alkanediyl_{(C\leq6)}-Y_1$. In some embodiments, the $alkanediyl_{(C\leq6)}$ is $-CH_2CH_2-$. In some embodiments, Y_1 is hydroxy or $aralkoxy_{(C\leq12)}$. In other embodiments, Y_1 $-OCH_2C_6H_5$.

In some embodiments, R_5 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups; $-alkanediyl_{(C\leq6)}-Y_2$; $-arenediyl_{(C\leq8)}-Y_3$; or $-arenediyl_{(C\leq8)}-alkanediyl_{(C\leq6)}-Y_4$, wherein Y_2, Y_3, and Y_4 are each independently: hydroxy, amino, halo, cyano, or

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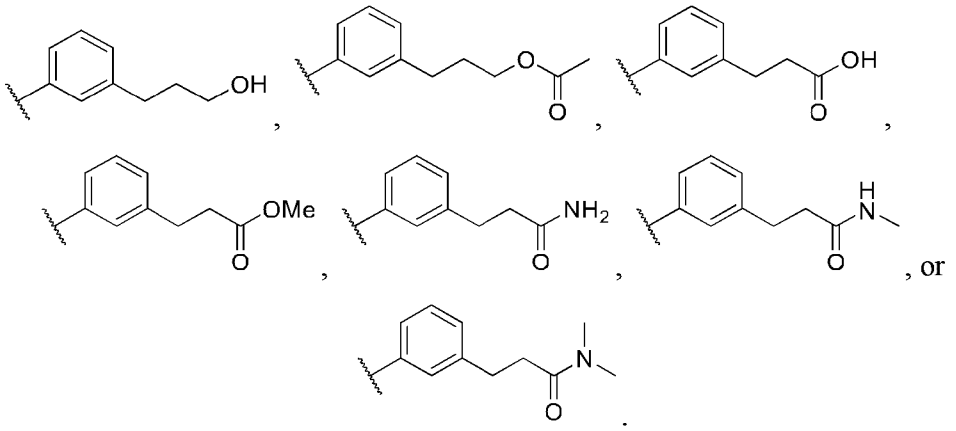
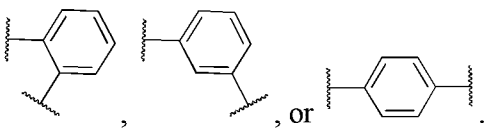
acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups.In some embodiments, R_5 is hydrogen. In other embodiments, R_5 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In some embodiments, R_5 is $-CH_2CH_2CH_2OCH_3$. In other embodiments, R_5 is aryl$_{(C\leq12)}$. In some embodiments, R_5 is phenyl, 2-methylphenyl, 1,1′-biphenyl-4-yl, or 1,1′-biphenyl-4-yl. In other embodiments, R_5 is substituted aryl$_{(C\leq12)}$. In some embodiments, R_5 is



, or .

In other embodiments, R_5 is heteroaryl$_{(C\leq12)}$. In some embodiments, R_5 is 4-(1-methyl)pyrazolyl or 5-(2-methyl)tetrazolyl. In other embodiments, R_5 is −alkanediyl$_{(C\leq6)}$−Y_2. In some embodiments, the alkanediyl$_{(C\leq6)}$ is $-CH_2CH_2CH_2-$. In some embodiments, Y_2 is methoxy. In other embodiments, R_5 is −arenediyl$_{(C\leq8)}$−Y_3. In some embodiments, the arenediyl$_{(C\leq8)}$ is:



, , or .

In some embodiments, Y_3 is alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, or substituted versions thereof. In some embodiments, Y_3 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In other embodiments, Y_3 is aryl$_{(C\leq12)}$. In some embodiments, Y_3 is phenyl. In other embodiments, Y_3 is heteroaryl$_{(C\leq12)}$. In some embodiments, Y_3 is 5-pyrimidinyl or 4-(1-methyl)pyrazolyl. In other embodiments, R_5 is −arenediyl$_{(C\leq8)}$−alkanediyl$_{(C\leq6)}$−Y_4. In some embodiments, the alkanediyl$_{(C\leq6)}$ is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$. In some embodiments, Y_4 is –OH. In other embodiments, Y_4 is acyl$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, or substituted acyloxy$_{(C\leq12)}$. In some embodiments, Y_4 is

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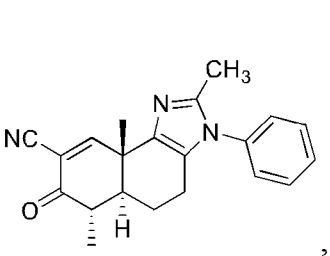
$-OC(O)CH_3$, $-NHC(O)CH_3$, $-CO_2H$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, or $-CO_2CH_3$.

In some embodiments, R_6 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$. In some embodiments, R_6 is methyl. In other embodiments, R_6 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$. In some embodiments, the carbon atom labeled 4 is in the S configuration. In some embodiments, the carbon atom labeled 5 is in the S configuration. In some embodiments, the carbon atom labeled 10 is in the R configuration.

In some embodiments, the compound is further defined as: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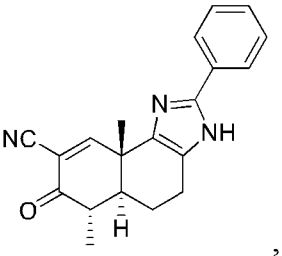
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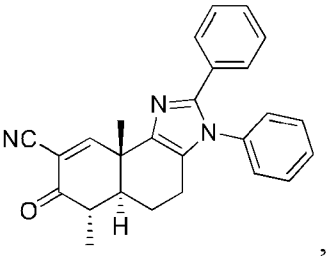
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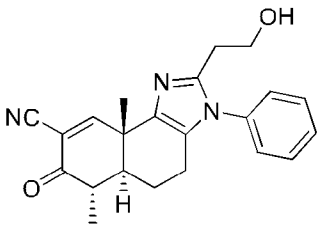
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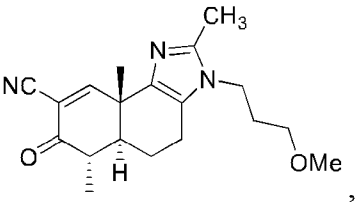
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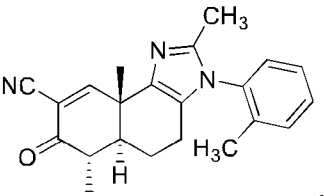
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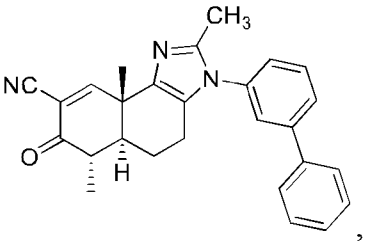
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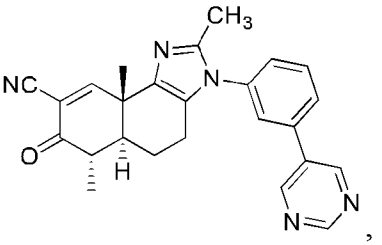
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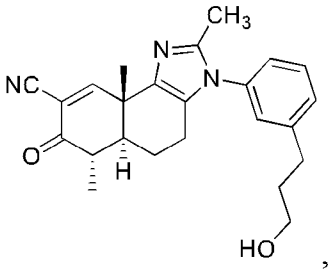
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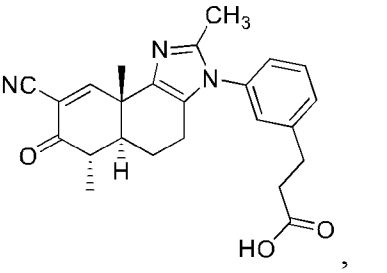
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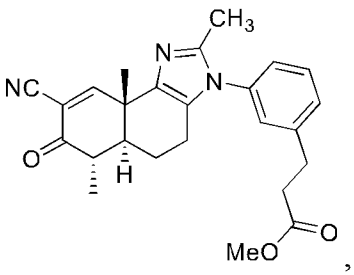
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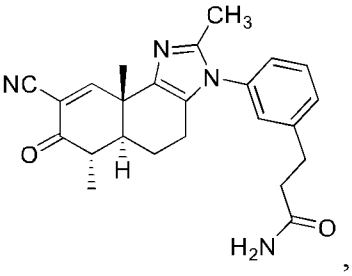
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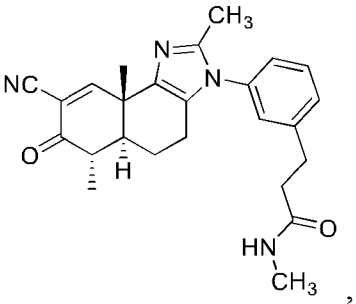
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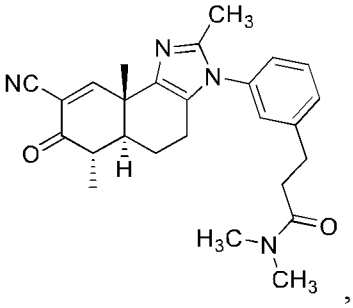
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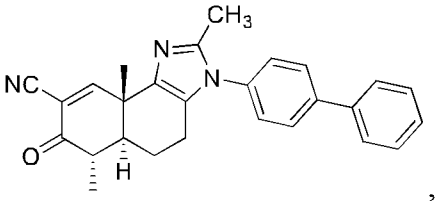
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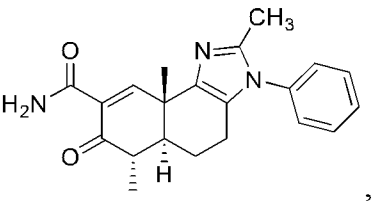
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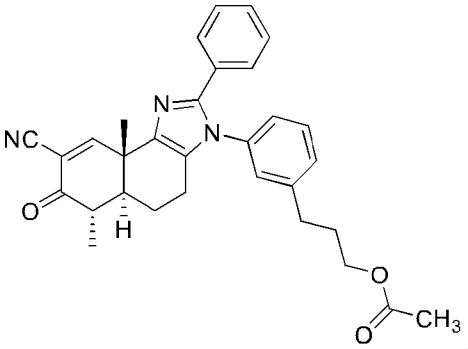
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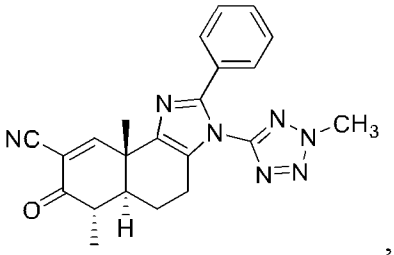
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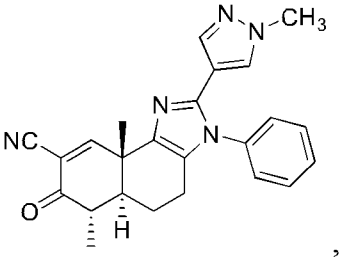
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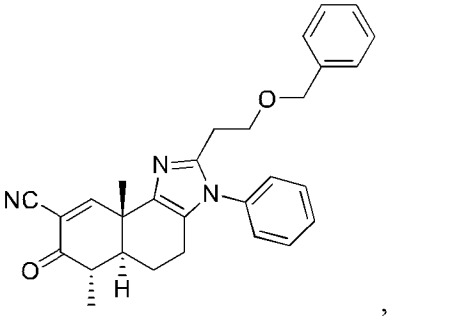
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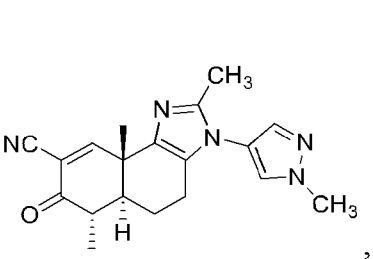
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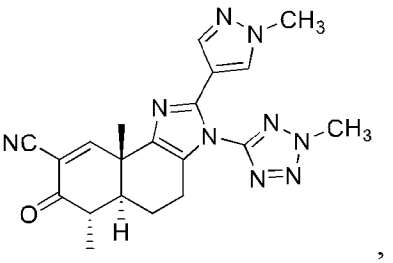
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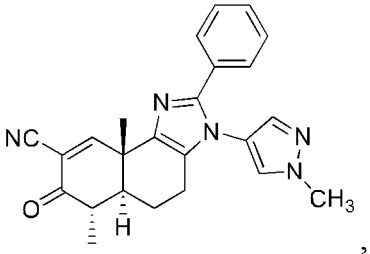
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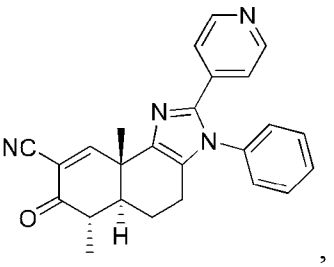
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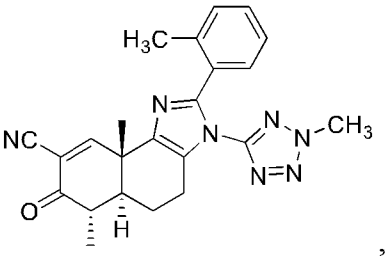
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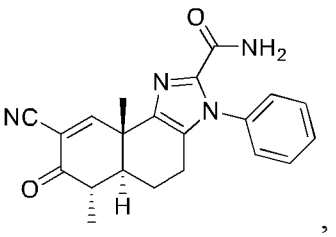
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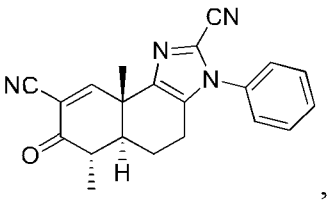
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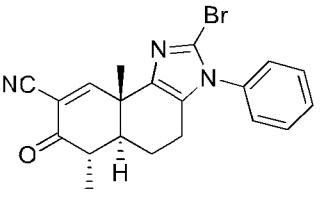

or a pharmaceutically acceptable salt of any of these formulas. In still further embodiments, the compound is further defined as:

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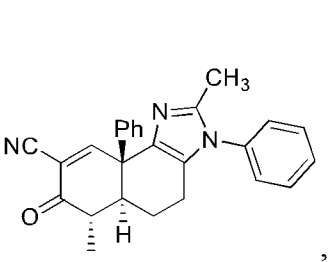

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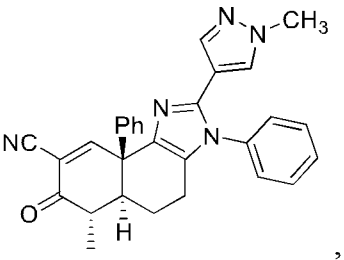

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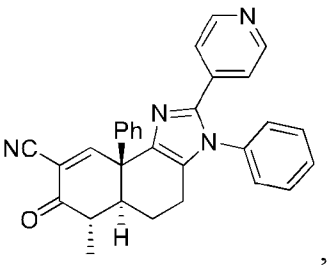

,

or a pharmaceutically acceptable salt of any of these formulas.

In yet another aspect, the present disclosure provides a pharmaceutical composition comprising:

a) a compound of the present disclosure; and

b) an excipient.

In still another aspect, the present disclosure provides a method of treating a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition of the present disclosure. In some embodiments, the patient is a human, primate, horse, cow, sheep, goat, guinea pig, dog, cat, rat, or mouse. In some embodiments, the patient is a human. In some embodiments, the disease or disorder is associated with inflammation. In some embodiments, the disease or disorder is characterized by overexpression of iNOS genes in the patient. In some embodiments, the disease or disorder is characterized by overexpression of COX-2 genes in the patient.

In still yet another aspect, the present disclosure provides a method of inhibiting nitric oxide production comprising administering to a patient in need thereof an amount of the compound or composition of the present disclosure sufficient to cause inhibition of IFN-γ-induced nitric oxide production in one or more cells of the patient.

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

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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.

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DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Disclosed herein are new compounds and compositions with antioxidant and/or anti-inflammatory properties, methods for their manufacture, and methods for their use, including for the treatment and/or prevention of disease.

I. Compounds and Synthetic Methods

The compounds provided by 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 *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2013). In addition, the synthetic methods may be further modified and optimized for preparative, pilot- or large-scale production, either batch of 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 *Practical Process Research & Development* (2012).

Compounds of the 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.

Chemical formulas used to represent compounds of the 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.

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Compounds of the invention may also 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.

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).

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

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solid forms of the compounds provided herein, including any solvates thereof are within the scope of the present invention.

II. Diseases Associated with Inflammation and/or Oxidative Stress

Inflammation is a biological process that provides resistance to infectious or parasitic organisms and the repair of damaged tissue. Inflammation is commonly characterized by localized vasodilation, redness, swelling, and pain, the recruitment of leukocytes to the site of infection or injury, production of inflammatory cytokines such as TNF-α and IL-1, and production of reactive oxygen or nitrogen species such as hydrogen peroxide, superoxide and peroxynitrite. In later stages of inflammation, tissue remodeling, angiogenesis, and scar formation (fibrosis) may occur as part of the wound healing process. Under normal circumstances, the inflammatory response is regulated and temporary and is resolved in an orchestrated fashion once the infection or injury has been dealt with adequately. However, acute inflammation can become excessive and life-threatening if regulatory mechanisms fail. Alternatively, inflammation can become chronic and cause cumulative tissue damage or systemic complications. In some embodiments, the compounds of this invention may be used in the treatment or prevention of inflammation or diseases associated with inflammation. Assay results for the suppression of IFNγ-induced NO production are presented in Example 1 below.

Many serious and intractable human diseases involve dysregulation of inflammatory processes, including diseases such as cancer, atherosclerosis, and diabetes, which were not traditionally viewed as inflammatory conditions. In the case of cancer, the inflammatory processes are associated with tumor formation, progression, metastasis, and resistance to therapy. Atherosclerosis, long viewed as a disorder of lipid metabolism, is now understood to be primarily an inflammatory condition, with activated macrophages playing an important role in the formation and eventual rupture of atherosclerotic plaques. Activation of inflammatory signaling pathways has also been shown to play a role in the development of insulin resistance, as well as in the peripheral tissue damage associated with diabetic hyperglycemia. Excessive production of reactive oxygen species and reactive nitrogen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite is a hallmark of inflammatory conditions. Evidence of dysregulated peroxynitrite production has been

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reported in a wide variety of diseases (Szabo *et al.*, 2007; Schulz *et al.*, 2008; Forstermann, 2006; Pall, 2007).

Autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis, and multiple sclerosis involve inappropriate and chronic activation of inflammatory processes in affected tissues, arising from dysfunction of self vs. non-self recognition and response mechanisms in the immune system. In neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, neural damage is correlated with activation of microglia and elevated levels of pro-inflammatory proteins such as inducible nitric oxide synthase (iNOS). Chronic organ failure such as renal failure, heart failure, liver failure, and chronic obstructive pulmonary disease is closely associated with the presence of chronic oxidative stress and inflammation, leading to the development of fibrosis and eventual loss of organ function. Oxidative stress in vascular endothelial cells, which line major and minor blood vessels, can lead to endothelial dysfunction and is believed to be an important contributing factor in the development of systemic cardiovascular disease, complications of diabetes, chronic kidney disease and other forms of organ failure, and a number of other aging-related diseases including degenerative diseases of the central nervous system and the retina.

Many other disorders involve oxidative stress and inflammation in affected tissues, including inflammatory bowel disease; inflammatory skin diseases; mucositis related to radiation therapy and chemotherapy; eye diseases such as uveitis, glaucoma, macular degeneration, and various forms of retinopathy; transplant failure and rejection; ischemia-reperfusion injury; chronic pain; degenerative conditions of the bones and joints including osteoarthritis and osteoporosis; asthma and cystic fibrosis; seizure disorders; and neuropsychiatric conditions including schizophrenia, depression, bipolar disorder, post-traumatic stress disorder, attention deficit disorders, autism-spectrum disorders, and eating disorders such as anorexia nervosa. Dysregulation of inflammatory signaling pathways is believed to be a major factor in the pathology of muscle wasting diseases including muscular dystrophy and various forms of cachexia.

A variety of life-threatening acute disorders also involve dysregulated inflammatory signaling, including acute organ failure involving the pancreas, kidneys, liver, or lungs, myocardial infarction or acute coronary syndrome, stroke, septic shock, trauma, severe burns, and anaphylaxis.

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Many complications of infectious diseases also involve dysregulation of inflammatory responses. Although an inflammatory response can kill invading pathogens, an excessive inflammatory response can also be quite destructive and in some cases can be a primary source of damage in infected tissues. Furthermore, an excessive inflammatory response can also lead to systemic complications due to overproduction of inflammatory cytokines such as TNF-α and IL-1. This is believed to be a factor in mortality arising from severe influenza, severe acute respiratory syndrome, and sepsis.

The aberrant or excessive expression of either iNOS or cyclooxygenase-2 (COX-2) has been implicated in the pathogenesis of many disease processes. For example, it is clear that NO is a potent mutagen (Tamir and Tannebaum, 1996), and that nitric oxide can also activate COX-2 (Salvemini *et al.*, 1994). Furthermore, there is a marked increase in iNOS in rat colon tumors induced by the carcinogen, azoxymethane (Takahashi *et al.*, 1997). A series of synthetic triterpenoid analogs of oleanolic acid have been shown to be powerful inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda *et al.* (2000a); Honda *et al.* (2000b), and Honda *et al.* (2002).

In one aspect, compounds disclosed herein are characterized by their ability to inhibit the production of nitric oxide in macrophage-derived RAW 264.7 cells induced by exposure to γ-interferon. They are further characterized by their ability to induce the expression of antioxidant proteins such as NQO1 and reduce the expression of pro-inflammatory proteins such as COX-2 and inducible nitric oxide synthase (iNOS). These properties are relevant to the treatment of a wide array of diseases and disorders involving oxidative stress and dysregulation of inflammatory processes including cancer, complications from localized or total-body exposure to ionizing radiation, mucositis resulting from radiation therapy or chemotherapy, autoimmune diseases, cardiovascular diseases including atherosclerosis, ischemia-reperfusion injury, acute and chronic organ failure including renal failure and heart failure, respiratory diseases, diabetes and complications of diabetes, severe allergies, transplant rejection, graft-versus-host disease, neurodegenerative diseases, diseases of the eye and retina, acute and chronic pain, degenerative bone diseases including

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osteoarthritis and osteoporosis, inflammatory bowel diseases, dermatitis and other skin diseases, sepsis, burns, seizure disorders, and neuropsychiatric disorders.

Without being bound by theory, the activation of the antioxidant/anti-inflammatory Keap1/Nrf2/ARE pathway is believed to be implicated in both the anti-inflammatory and anti-carcinogenic properties of the compounds disclosed herein.

In another aspect, compounds disclosed herein may be used for treating a subject having a condition caused by elevated levels of oxidative stress in one or more tissues. Oxidative stress results from abnormally high or prolonged levels of reactive oxygen species such as superoxide, hydrogen peroxide, nitric oxide, and peroxynitrite (formed by the reaction of nitric oxide and superoxide). The oxidative stress may be accompanied by either acute or chronic inflammation. The oxidative stress may be caused by mitochondrial dysfunction, by activation of immune cells such as macrophages and neutrophils, by acute exposure to an external agent such as ionizing radiation or a cytotoxic chemotherapy agent (*e.g.*, doxorubicin), by trauma or other acute tissue injury, by ischemia/reperfusion, by poor circulation or anemia, by localized or systemic hypoxia or hyperoxia, by elevated levels of inflammatory cytokines and other inflammation-related proteins, and/or by other abnormal physiological states such as hyperglycemia or hypoglycemia.

In animal models of many such conditions, stimulating expression of inducible heme oxygenase (HO-1), a target gene of the Nrf2 pathway, has been shown to have a significant therapeutic effect including models of myocardial infarction, renal failure, transplant failure and rejection, stroke, cardiovascular disease, and autoimmune disease (*e.g.*, Sacerdoti *et al.*, 2005; Abraham & Kappas, 2005; Bach, 2006; Araujo *et al.*, 2003; Liu *et al.*, 2006; Ishikawa *et al.*, 2001; Kruger *et al.*, 2006; Satoh *et al.*, 2006; Zhou *et al.*, 2005; Morse and Choi, 2005; Morse and Choi, 2002). This enzyme breaks free heme down into iron, carbon monoxide (CO), and biliverdin (which is subsequently converted to the potent antioxidant molecule, bilirubin).

In another aspect, compounds of this invention may be used in preventing or treating tissue damage or organ failure, acute and chronic, resulting from oxidative stress exacerbated by inflammation. Examples of diseases that fall in this category include: heart failure, liver failure, transplant failure and rejection, renal failure, pancreatitis, fibrotic lung diseases (cystic fibrosis and COPD, among others), diabetes (including complications), atherosclerosis, ischemia-reperfusion injury, glaucoma, stroke, autoimmune disease, autism, macular degeneration, and muscular dystrophy.

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For example, in the case of autism, studies suggest that increased oxidative stress in the central nervous system may contribute to the development of the disease (Chauhan and Chauhan, 2006).

Evidence also links oxidative stress and inflammation to the development and pathology of many other disorders of the central nervous system, including psychiatric disorders such as psychosis, major depression, and bipolar disorder; seizure disorders such as epilepsy; pain and sensory syndromes such as migraine, neuropathic pain or tinnitus; and behavioral syndromes such as the attention deficit disorders. See, *e.g.*, Dickerson *et al.*, 2007; Hanson *et al.*, 2005; Kendall-Tackett, 2007; Lencz *et al.*, 2007; Dudhgaonkar *et al.*, 2006; Lee *et al.*, 2007; Morris *et al.*, 2002; Ruster *et al.*, 2005; McIver *et al.*, 2005; Sarchielli *et al.*, 2006; Kawakami *et al.*, 2006; Ross *et al.*, 2003. For example, elevated levels of inflammatory cytokines, including TNF, interferon-γ, and IL-6, are associated with major mental illness (Dickerson *et al.*, 2007). Microglial activation has also been linked to major mental illness. Therefore, downregulating inflammatory cytokines and inhibiting excessive activation of microglia could be beneficial in patients with schizophrenia, major depression, bipolar disorder, autism-spectrum disorders, and other neuropsychiatric disorders.

Accordingly, in pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation, treatment may comprise administering to a subject a therapeutically effective amount of a compound of this invention, such as those described above or throughout this specification. Treatment may be administered preventively, in advance of a predictable state of oxidative stress (*e.g.*, organ transplantation or the administration of radiation therapy to a cancer patient), or it may be administered therapeutically in settings involving established oxidative stress and inflammation.

The compounds disclosed herein may be generally applied to the treatment of inflammatory conditions, such as sepsis, dermatitis, autoimmune disease and osteoarthritis. In one aspect, the compounds of this invention may be used to treat inflammatory pain and/or neuropathic pain, for example, by inducing Nrf2 and/or inhibiting NF-κB.

In some embodiments, the compounds disclosed herein may be used in the treatment and prevention of diseases such as cancer, inflammation, Alzheimer's

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disease, Parkinson's disease, multiple sclerosis, autism, amyotrophic lateral sclerosis, Huntington's disease, autoimmune diseases such as rheumatoid arthritis, lupus, Crohn's disease and psoriasis, inflammatory bowel disease, all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide or prostaglandins, and pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation.

Another aspect of inflammation is the production of inflammatory prostaglandins such as prostaglandin E. These molecules promote vasodilation, plasma extravasation, localized pain, elevated temperature, and other symptoms of inflammation. The inducible form of the enzyme COX-2 is associated with their production, and high levels of COX-2 are found in inflamed tissues. Consequently, inhibition of COX-2 may relieve many symptoms of inflammation and a number of important anti-inflammatory drugs (*e.g.*, ibuprofen and celecoxib) act by inhibiting COX-2 activity. Recent research, however, has demonstrated that a class of cyclopentenone prostaglandins (cyPGs) (*e.g.*, 15-deoxy prostaglandin J2, a.k.a. PGJ2) plays a role in stimulating the orchestrated resolution of inflammation (*e.g.*, Rajakariar *et al.*, 2007). COX-2 is also associated with the production of cyclopentenone prostaglandins. Consequently, inhibition of COX-2 may interfere with the full resolution of inflammation, potentially promoting the persistence of activated immune cells in tissues and leading to chronic, "smoldering" inflammation. This effect may be responsible for the increased incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long periods of time.

In one aspect, the compounds disclosed herein may be used to control the production of pro-inflammatory cytokines within the cell by selectively activating regulatory cysteine residues (RCRs) on proteins that regulate the activity of redox-sensitive transcription factors. Activation of RCRs by cyPGs has been shown to initiate a pro-resolution program in which the activity of the antioxidant and cytoprotective transcription factor Nrf2 is potently induced and the activities of the pro-oxidant and pro-inflammatory transcription factors NF-κB and the STATs are suppressed. In some embodiments, this increases the production of antioxidant and reductive molecules (NQO1, HO-1, SOD1, γ-GCS) and decreases oxidative stress and the production of pro-oxidant and pro-inflammatory molecules (iNOS, COX-2, TNF-α). In some embodiments, the compounds of this invention may cause the cells that host the

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inflammatory event to revert to a non-inflammatory state by promoting the resolution of inflammation and limiting excessive tissue damage to the host.

III. Pharmaceutical Formulations and Routes of Administration

For administration to an animal especially a mammal in need of such treatment, the compounds in a therapeutically effective amount are ordinarily combined with one or more excipients appropriate to the indicated route of administration. The compounds of the present invention are contemplated to be formulated in a manner ameniable to treatment of a veterinary patient as well as a human patient. In some embodiments, the veterinary patient may be a companion animal, livestock animals, zoo animals, and wild animals The compounds may be admixed with 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, and tableted or encapsulated for convenient administration. Alternatively, the compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other excipients and modes of administration are well and widely known in the pharmaceutical art and may be adapted to the type of animal being treated.

The pharmaceutical compositions useful in the present invention may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional pharmaceutical carriers and excipients such as preservatives, stabilizers, wetting agents, emulsifiers, buffers, *etc*.

The compounds of the present disclosure 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 active compounds may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. They may also be administered by continuous perfusion/infusion of a disease or wound site.

To administer the therapeutic 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 therapeutic compound may be administered to a patient in an appropriate carrier, for example,

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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 therapeutic compound 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 may be 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. In all cases, the composition must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. 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.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile carrier which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient (*i.e.*,

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the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The therapeutic compound can be orally administered, for example, with an inert diluent or an assimilable edible carrier. The therapeutic compound 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 therapeutic compound 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 therapeutically useful compositions is such that a suitable dosage will be obtained.

It is especially 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. 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.

The therapeutic compound may also be administered topically to the skin, eye, or mucosa. Alternatively, if local delivery to the lungs is desired the therapeutic compound may be administered by inhalation in a dry-powder or aerosol formulation.

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, such as the model systems shown in the examples and drawings.

An effective dose range of a therapeutic 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):

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(a) HED (mg/kg) = Animal dose (mg/kg) × (Animal K_m/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.

An 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 1.0 mg/kg to about 250 mg/kg, from about 10.0 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 10000 mg per day, 100 mg to 10000 mg per day, 500 mg to 10000 mg per day, and 500 mg to 1000 mg per day. In some particular embodiments, the amount is less than 10,000 mg per day with a range of 750 mg to 9000 mg per day.

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The effective amount may be less than 1 mg/kg/day, less than 500 mg/kg/day, less than 250 mg/kg/day, less than 100 mg/kg/day, less than 50 mg/kg/day, less than 25 mg/kg/day or less than 10 mg/kg/day. It may alternatively be in the range of 1 mg/kg/day to 200 mg/kg/day. For example, regarding treatment of diabetic patients, the unit dosage may be an amount that reduces blood glucose by at least 40% as compared to an untreated subject. In another embodiment, the unit dosage is an amount that reduces blood glucose to a level that is ± 10% of the blood glucose level of a non-diabetic subject.

In other non-limiting examples, a dose may also comprise from about 1 microgram/kg/body weight, about 5 microgram/kg/body weight, about 10 microgram/kg/body weight, about 50 microgram/kg/body weight, about 100 microgram/kg/body weight, about 200 microgram/kg/body weight, about 350 microgram/kg/body weight, about 500 microgram/kg/body weight, about 1 milligram/kg/body weight, about 5 milligram/kg/body weight, about 10 milligram/kg/body weight, about 50 milligram/kg/body weight, about 100 milligram/kg/body weight, about 200 milligram/kg/body weight, about 350 milligram/kg/body weight, about 500 milligram/kg/body weight, to about 1000 mg/kg/body weight or more per administration, and any range derivable therein. In non-limiting examples of a derivable range from the numbers listed herein, a range of about 5 milligram/kg/body weight to about 100 milligram/kg/body weight, about 5 microgram/kg/body weight to about 500 milligram/kg/body weight, *etc.*, can be administered, based on the numbers described above.

In certain embodiments, a pharmaceutical composition of the present disclosure may comprise, for example, at least about 0.1% of a compound of the present disclosure. In other embodiments, the compound of the present disclosure may comprise between about 2% to about 75% of the weight of the unit, or between about 25% to about 60%, for example, and any range derivable therein.

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

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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).

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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, for example, the formula  includes  ,  ,  ,  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.

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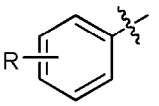
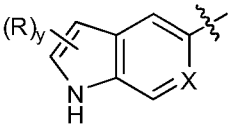
When a group "R" is depicted as a "floating group" on a ring system, for example, in the formula:



,

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



,

then R 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 group "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, *e.g.*, it is understood that the minimum number of carbon atoms in the group "alkenyl$_{(C\leq 8)}$" or the class "alkene$_{(C\leq 8)}$" is two. Compare with "alkoxy$_{(C\leq 10)}$", which designates alkoxy groups having from 1 to 10 carbon atoms. "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

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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(s) in a moiety replacing a hydrogen atom is not counted. Thus methoxyhexyl, which has a total of seven carbon atoms, is an example of a substituted alkyl$_{(C1-6)}$.

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" when used without the "substituted" modifier signifies that the compound or chemical group so modified is an acyclic or cyclic, but non-aromatic hydrocarbon 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" when used to modify a compound or a chemical group refers to a 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

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$-CH_2C(CH_3)_3$ (*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, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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). 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

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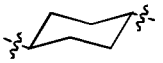
carbon and hydrogen. The group  is a non-limiting example of cycloalkanediyl group. A "cycloalkane" refers to the class of compounds having the formula H−R, wherein R is cycloalkyl as this term is defined above. When any of these terms is used with the "substituted" modifier one or more hydrogen atom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

The term "alkenyl" when used without the "substituted" modifier refers to an 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, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$. The groups −CH=CHF, −CH=CHCl and −CH=CHBr are non-limiting examples of substituted alkenyl groups.

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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 $-C\equiv CH$, $-C\equiv CCH_3$, and $-CH_2C\equiv CCH_3$ 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 $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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 six-membered aromatic ring structure, wherein the ring atoms 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. As used herein, the term does not preclude the presence of one or more alkyl or aralkyl 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. 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 structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. As used herein, the term does not preclude the presence of one or more alkyl, aryl 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 may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). Non-limiting examples of arenediyl groups include:

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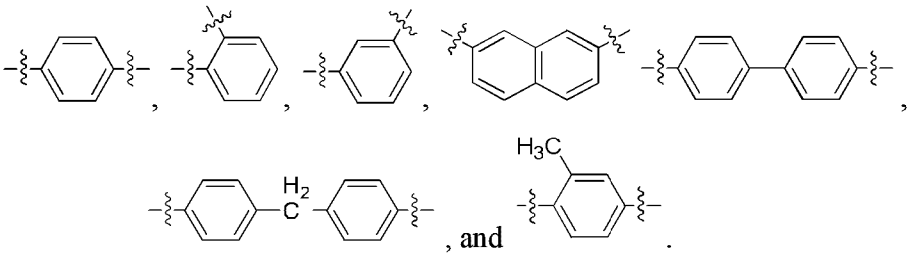

An "arene" refers to the class of compounds having the formula H–R, wherein R is aryl as that term is defined above. Benzene and toluene are non-limiting examples of arenes. When any of these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, –CN, –SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, –CN, –SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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 wherein at least one of the ring atoms 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 may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl, aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the aromatic ring or aromatic ring system. Non-limiting examples of heteroaryl groups include furanyl, imidazolyl, indolyl,

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indazolyl (Im), isoxazolyl, methylpyridinyl, oxazolyl, phenylpyridinyl, pyridinyl (pyridyl), pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, triazinyl, tetrazolyl, thiazolyl, thienyl, and triazolyl. 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 has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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 wherein at least one of the ring atoms 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 may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. 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 "*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 has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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, alkenyl, aryl, aralkyl or heteroaryl, as those terms are defined above. The groups, −CHO, $-C(O)CH_3$ (acetyl,

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Ac), $-C(O)CH_2CH_3$, $-C(O)CH_2CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-C(O)CH(CH_2)_2$, $-C(O)C_6H_5$, $-C(O)C_6H_4CH_3$, $-C(O)CH_2C_6H_5$, and $-C(O)$(imidazolyl) 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 alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with 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 $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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), $-OC(CH_3)_3$ (*tert*-butoxy), $-OCH(CH_2)_2$, $-O-$cyclopentyl, and $-O-$cyclohexyl. 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 $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$.

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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, or R and R′ can be taken together to represent an alkanediyl. 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", "alkoxyamino", and "alkylsulfonylamino" when used without the "substituted" modifier, refers to groups, defined as −NHR, in which R is cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, alkoxy, and alkylsulfonyl, 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 $-NHC(O)CH_3$. The term "alkylimino" when used without the "substituted" modifier refers to the divalent group =NR, in which R is an alkyl, as that term is defined above. 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, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, 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.

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

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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 a disease, is sufficient to effect such treatment for 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. 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.

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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, horse, 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 subjects 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

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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).

The term "pharmaceutically acceptable carrier," as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

"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.

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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 $\leq$ 15%, more preferably $\leq$ 10%, even more preferably $\leq$ 5%, or most preferably $\leq$ 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 in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

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Other abbreviations used herein are as follows: DMSO, dimethyl sulfoxide; 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; HO-1, inducible heme oxygenase.

The fact that certain terms are defined 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: Nitric Oxide Production Assays

Tissue Culture: RAW 264.7, a mouse macrophage cell line, was obtained from American Type Culture Collection (Manassas VA) and maintained in the log phase of growth in Dulbecco's Modified Eagle's Medium (DMEM), 10% heat inactivated fetal calf serum and 100 units/mL antibiotic-antimycotic (AA). Cells were cultured and maintained in a humidified incubator at 37 °C under 5% CO_2 and 95% air. Cells were sub-cultured every 3 days by scraping and were not used beyond passage 20. All cell culture supplies were obtained from Life Technologies (Grand Island, NY).

Nitric Oxide Suppression Assay. RAW 264.7 cells were plated 1 day in advance of experiment at a concentration of 80,000 cells/well onto CellBIND® 96 well plates (Corning, NY) in a total volume of 100 µL. The next day, pre-treat cells with compounds (from 3 µM to 0.3 nM serially diluted in a 10 point curve) from a 10× stock by adding 10 µL per well in complete DMEM media containing 10% fetal calf serum. The plates were centrifuged for 3 minutes at 400×g at room temperature

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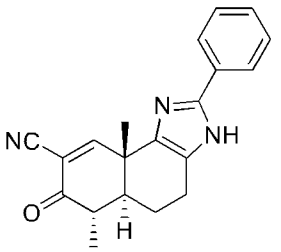
followed by 2 hour incubation at 37 °C. The cells were then incubated overnight at 37 °C with 10 µL of the insult, interferon gamma (R&D Systems, Minneapolis, MN), from a 10× stock for a final concentration of 20 ng/mL. The plates were centrifuged for 3 minutes at 400×g at room temperature followed by ~18 hour incubation at 37 °C. The following day, transfer 50 µL cell culture supernatant from each well into a clear bottom 96 well plate and follow the instructions from Promega's Griess Detection Kit #G2930 (Madison, WI) which involves the addition of 50 µL of the provided sulfanilamide solution for a 5-10 minute incubation at room temperature. Next add 50 µL of the provided *N*-1-napthylethylenediamine dihydrochloride (NED) solution for a 5-10 minute incubation at room temperature and protected from light. If any air bubbles were introduced into the well, the plates need to be centrifuged for 5 minutes at 400×g at room temperature to avoid interference with absorbance readings. The plates were read for absorbance within 30 minutes with a filter between 520 nm and 550 nm.

For the ability of compounds to suppress the increase in nitric oxide release, the percent maximal intensity of nitric oxide detected in each well was normalized to that induced by the peak value for 20 ng/mL of interferon gamma alone and plotted against the compound concentration to calculate IC_{50} values and to control for plate-to-plate variability. Concentration-response data were analyzed using GraphPad Prism (San Diego, CA); the IC_{50} values were derived from a single curve fit to the mean data of n=2-3, in duplicates. Selected data is shown in Table 1.

All compounds were dissolved in dimethyl sulfoxide at 10 mM stock solutions and tested at a concentration that the dimethyl sulfoxide levels never exceeded 1%.

Table 1: Nitric Oxide Inhibition

Compound Number	Structure	NO IC_{50} (nM)
T1		151

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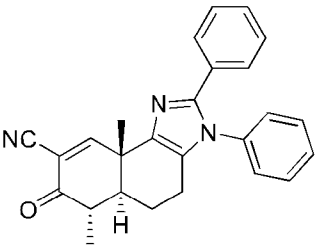
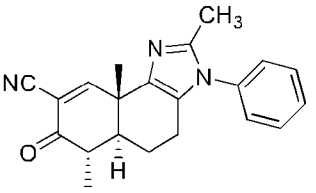
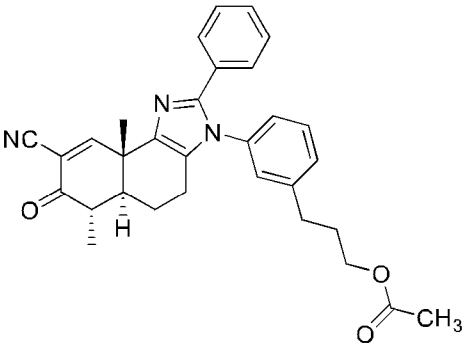
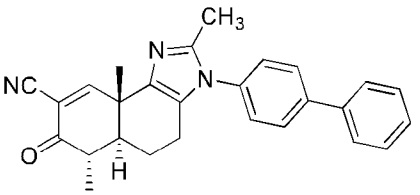
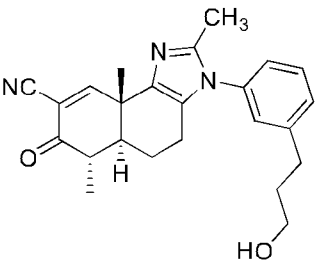
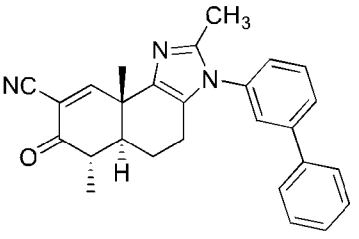
Compound Number	Structure	NO IC_{50} (nM)
T2		471
T3		40.8
T4		662
T5		136
T6		19.4
T7		91.8

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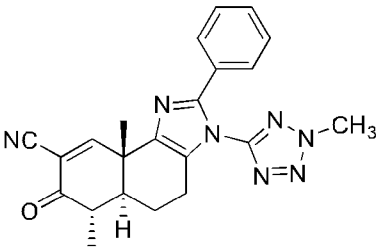
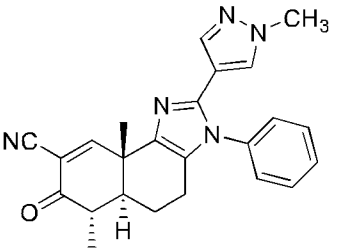
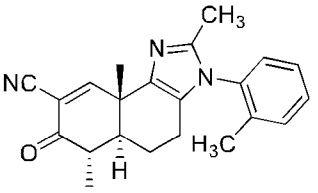
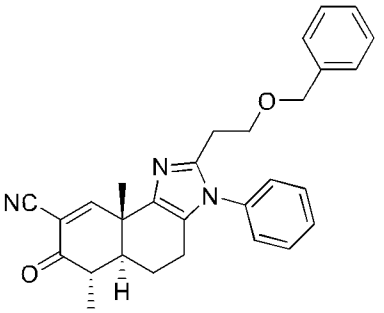
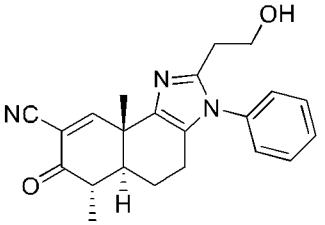
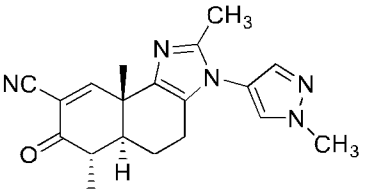
Compound Number	Structure	NO IC_{50} (nM)
T8		28.8
T9		22.7
T10		62.8
T11		93.2
T12		11.3
T13		233

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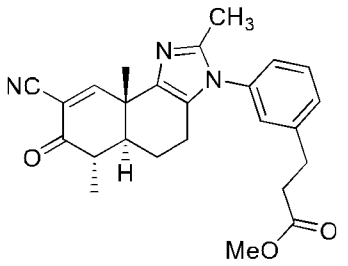
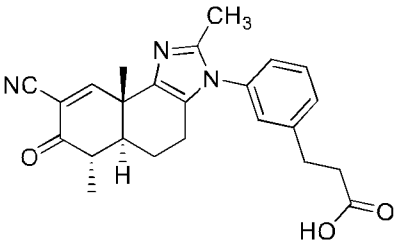
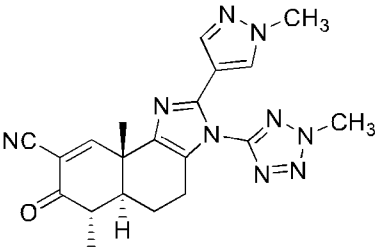
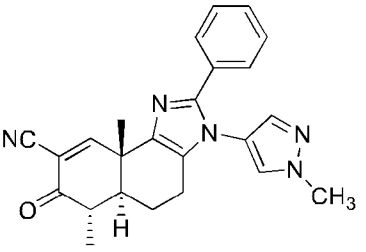
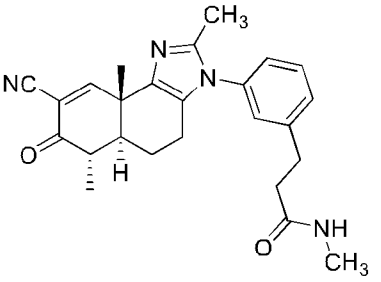
Compound Number	Structure	NO IC_{50} (nM)
T14		222
T15		>3000
T16		132
T17		120
T18		693

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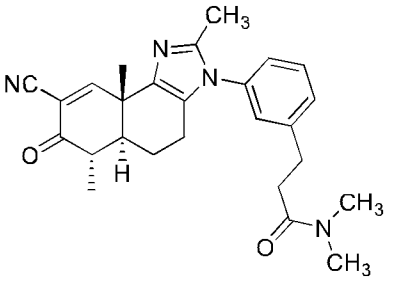
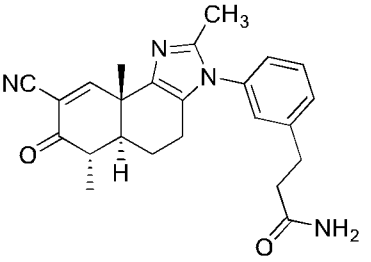
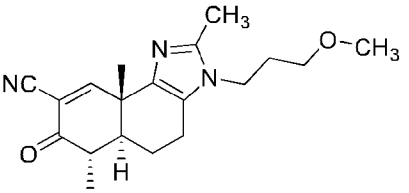
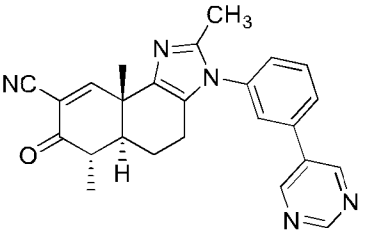
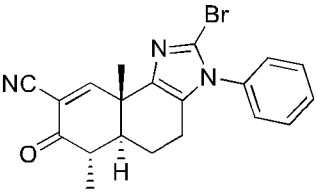
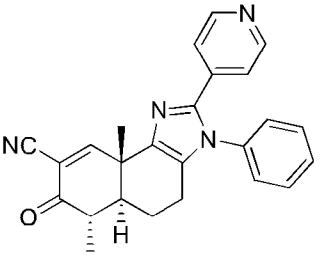
Compound Number	Structure	NO IC_{50} (nM)
T19		82.7
T20		1000
T21		407
T22		47.8
T23		31.1
T24		48.8

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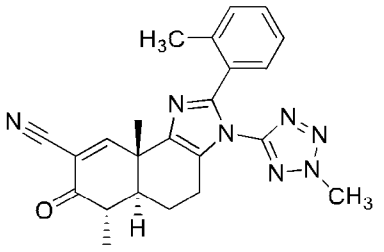
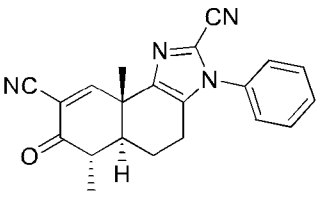
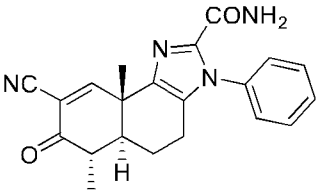
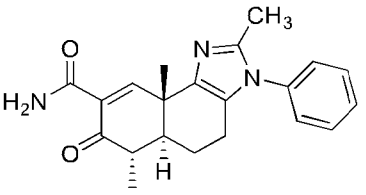
Compound Number	Structure	NO IC_{50} (nM)
T25		15.4
T26		27.7
T27		53.1
T28		138

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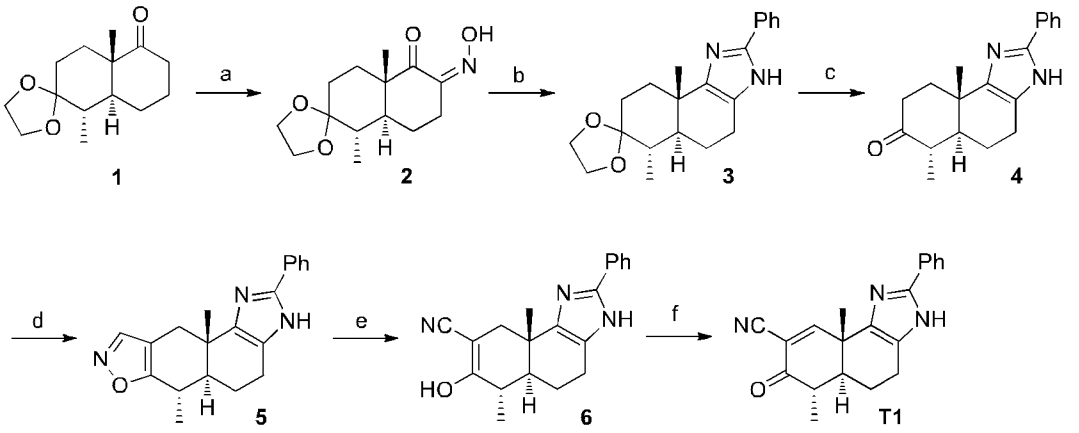
Example 2: Synthesis and Characterization

Scheme 1



Reagents and conditions: a) *t*-BuOK, *i*-amyl nitrite, THF, -30 °C to rt, 59%; b) benzylamine, 150 °C, 38%; c) $TsOH \cdot H_2O$, acetone, water, rt, 100%; d) i) HCO_2Et, NaOMe, MeOH, 0 °C to rt; ii) $NH_2OH \cdot HCl$, 1 N HCl, 55 °C, 69%; e) NaOMe, MeOH, 55 °C, 87%; f) i) DBDMH, DMF, 0 °C; ii) Py, 55 °C, 80%.

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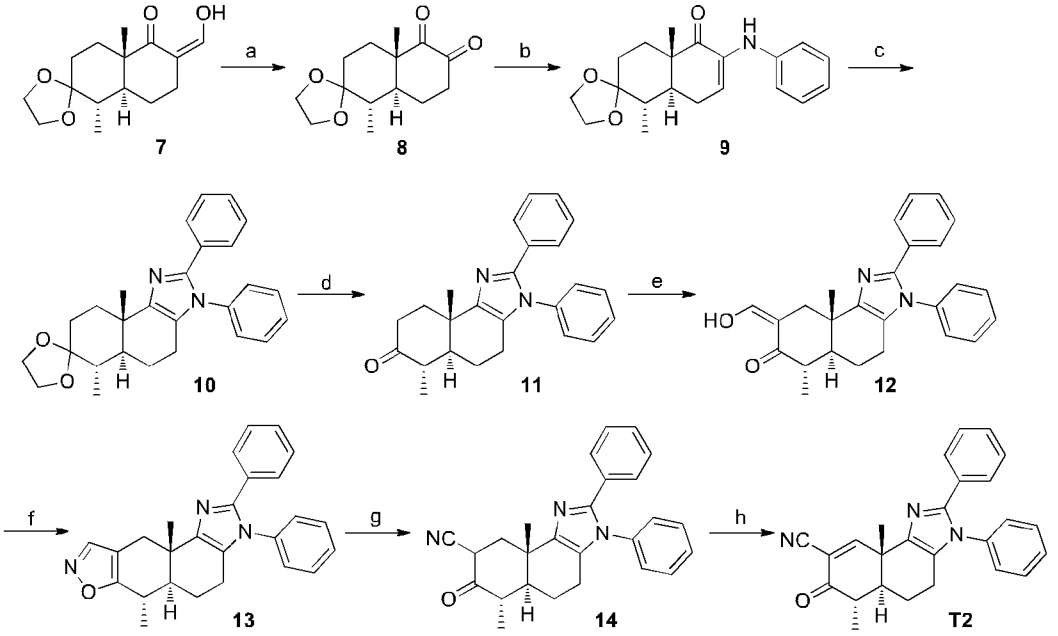
Scheme 2



Reagents and conditions: a) i) Ozone, CH_2Cl_2, -78 °C; ii) Me_2S, rt, 16 h, 98%; b) aniline, $TsOH \cdot H_2O$, benzene, reflux, 60%; c) benzaldehyde, NH_4OAc, EtOH, rt, 85%; d) aq. HCl, THF, rt; e) HCO_2Et, NaOMe, MeOH, rt; f) $NH_2OH \cdot HCl$, EtOH, 50 ºC; g) NaOMe, MeOH, THF, rt, 78% from **10**; h) i) Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 30%.

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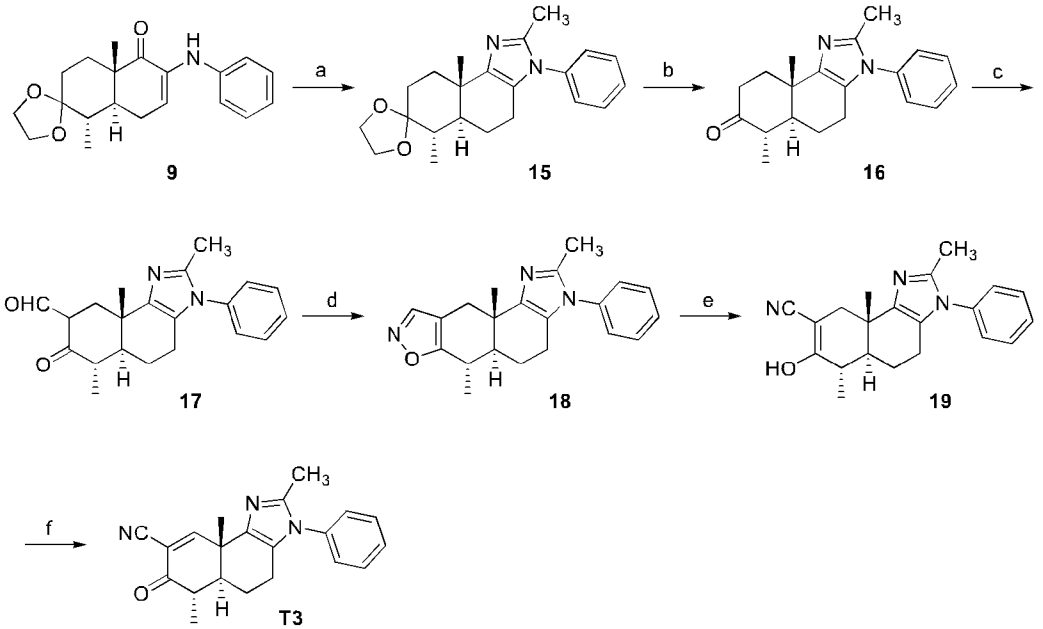
Scheme 3



Reagents and conditions: a) NH_4OAc, CH_3CHO, EtOH, rt, 80%: b) aq. HCl, MeOH, rt, 96%; c) HCO_2Et, NaOMe, MeOH, benzene, rt; d) $NH_2OH \cdot HCl$, EtOH, 50 °C to rt; e) NaOMe, MeOH, rt; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 50 °C, 28% from **16**.

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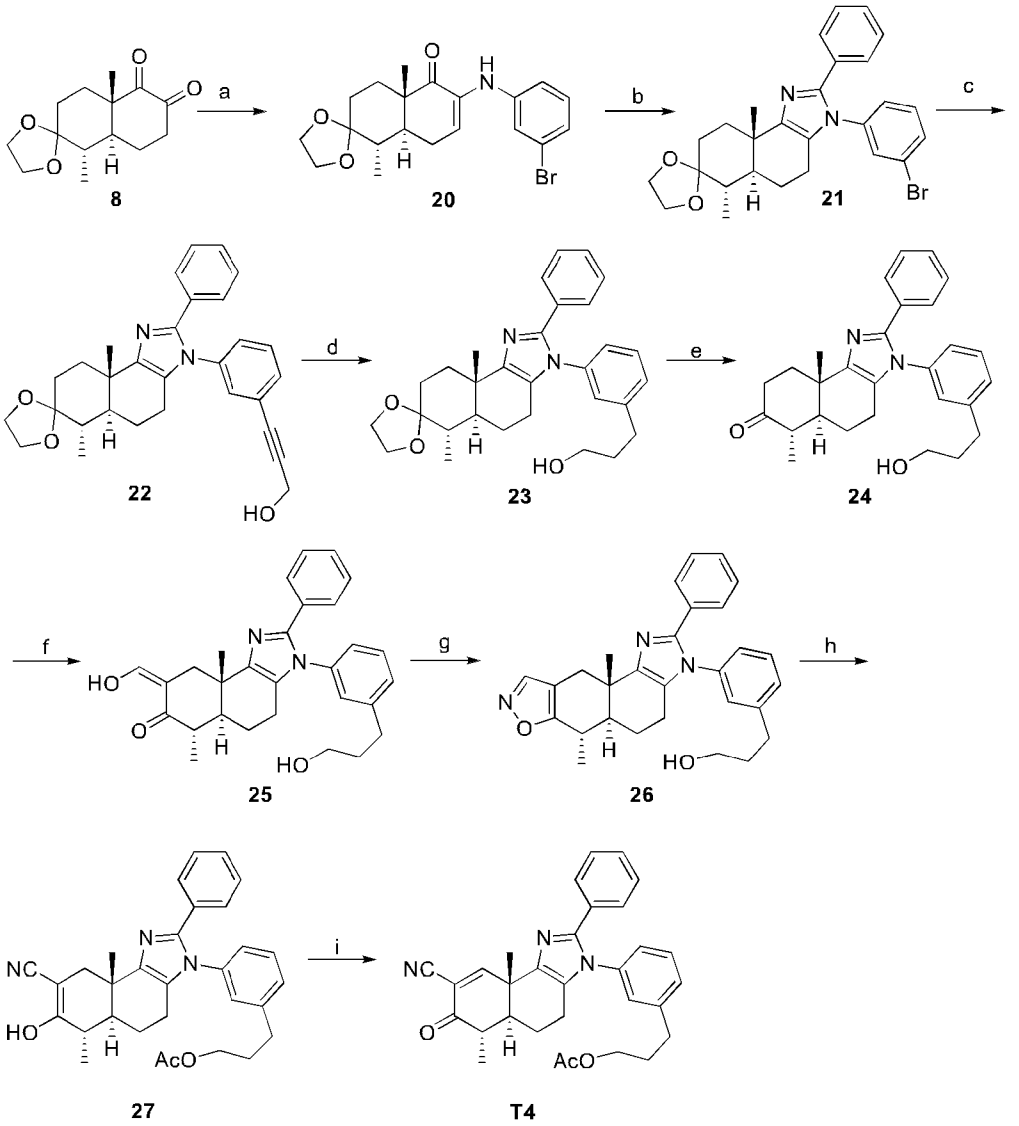
Scheme 4



Reagents and conditions: a) 3-bromoaniline,$TsOH \cdot H_2O$, benzene, reflux, 72%; b) benzaldehyde, NH_4OAc, EtOH, rt to 65 °C, 77%; c) CuI, Pd $(PPh_3)_2Cl_2$, propargyl alcohol, Et_3N, toluene, 80 ºC, 30%; d) 10% Pd/C, EtOAc, H_2, 1 atm, 67%; e) aq. HCl, THF, rt, 96%; f) HCO_2Et, NaOMe, rt, 96%; g) $NH_2OH \cdot HCl$, EtOH, 50 ºC, 96%; h) NaOMe, MeOH, THF, rt, 94%; i) i) Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 15%.

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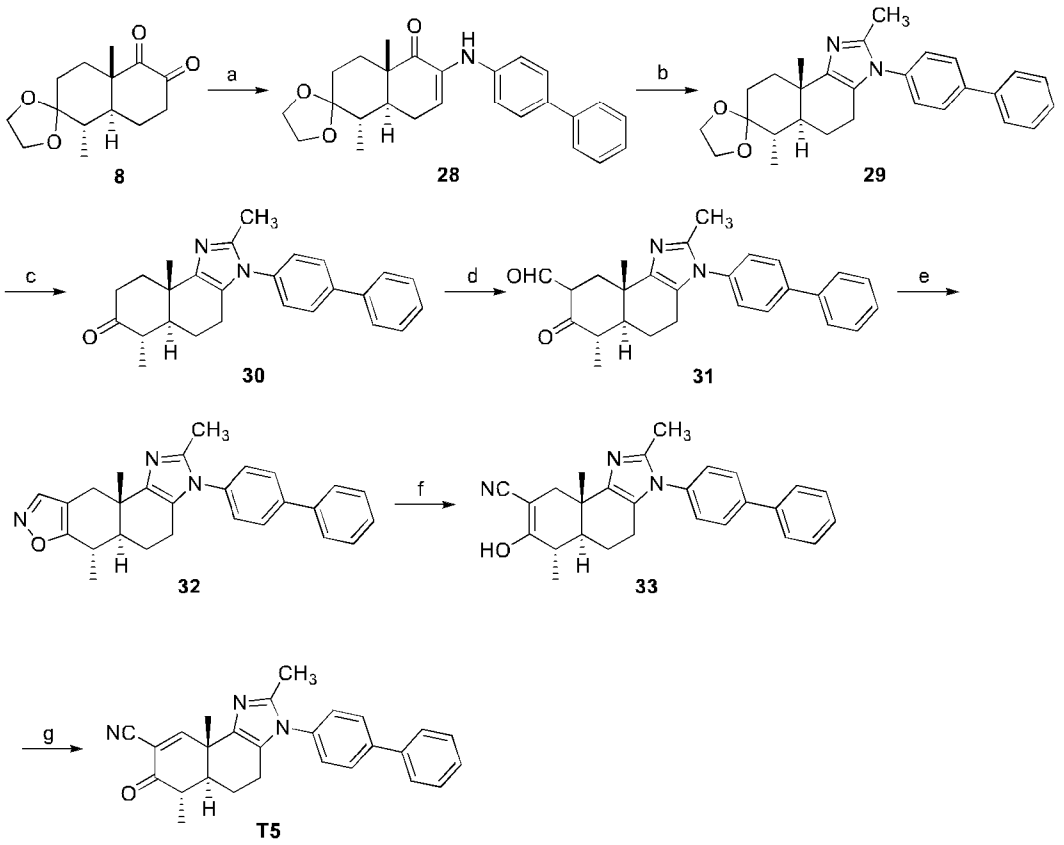
Scheme 5



Reagents and conditions: a) biphenyl-4-amine, $TsOH \cdot H_2O$, benzene, 80 ºC, 62%; b) NH_4OAc, CH_3CHO, THF, EtOH, rt, 76%: c) aq. HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, 0 ºC-rt; e) $NH_2OH \cdot HCl$, EtOH, 50 ºC to rt; f) NaOMe, THF, MeOH, rt, 76% from **29**; g) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 ºC, 57%.

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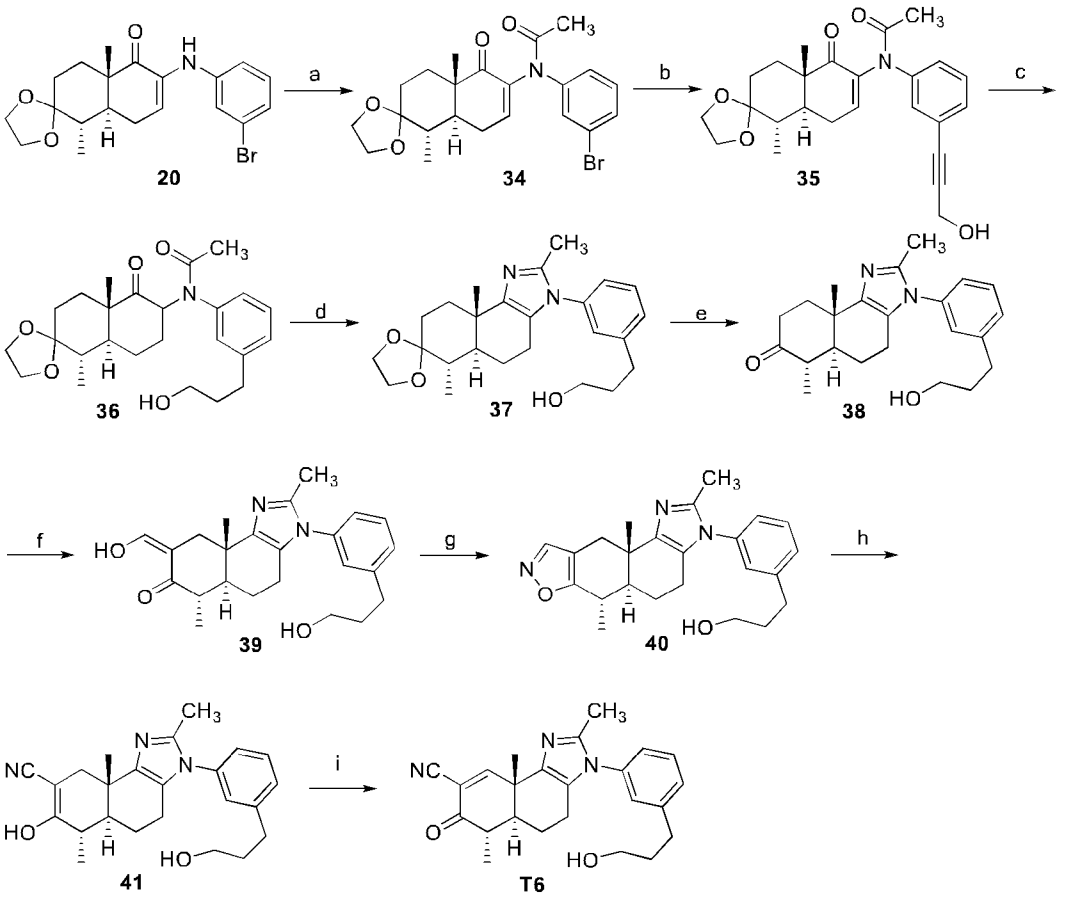
Scheme 6



Reagents and conditions: a) acetic anhydride, NaOAc,140 ºC, 35%; b) CuI, Pd $(PPh_3)_2Cl_2$, propargyl alcohol, Et_3N, DME, 80 ºC, 34%; c) 10% Pd/C, EtOAc, H_2, rt, 1 atm, 90%; d) MeCHO, NH_4OAc, EtOH, 90 ºC, 39%; e) aq. HCl, THF, rt, 100%; f) HCO_2Et, NaOMe, MeOH, rt, 82%; g) $NH_2OH{\cdot}HCl$, EtOH, 50 ºC, 100%; h) NaOMe, THF, MeOH, rt, 80%; i) i)Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 25%.

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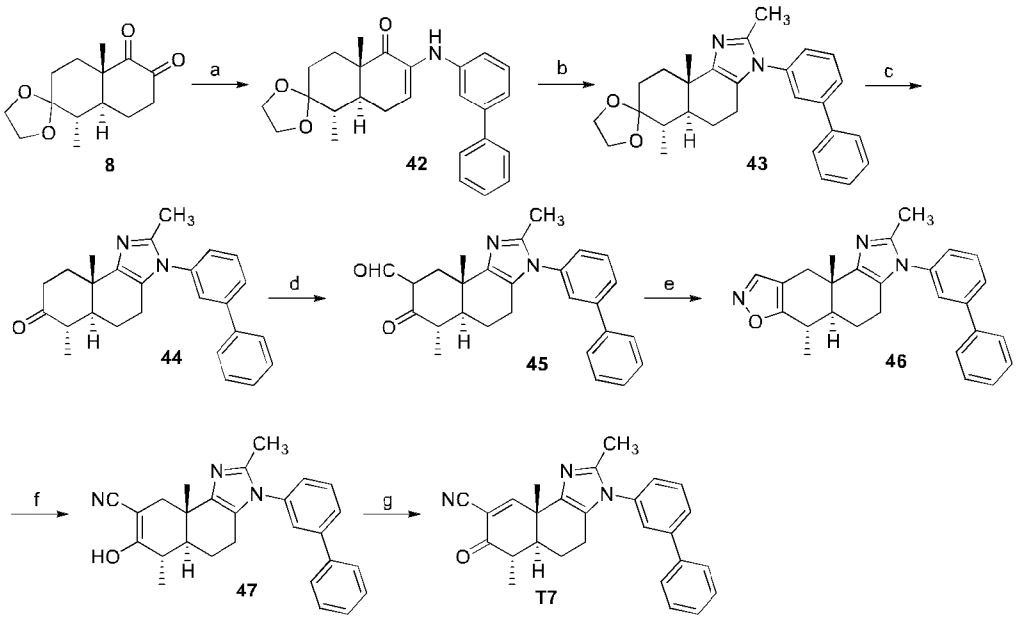
Scheme 7



Reagents and conditions: a) biphenyl-3-amine, $TsOH \cdot H_2O$, benzene, 80 ºC, 75%; b) NH_4OAc, CH_3CHO, THF, EtOH, rt, 74%: c) aq. HCl, THF, rt, 86%; d) HCO_2Et, NaOMe, MeOH, THF, 0 ºC to rt; e) $NH_2OH \cdot HCl$, EtOH, 50 ºC to rt; f) NaOMe, THF, MeOH, rt, 76% from **44**; g) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 ºC, 54%.

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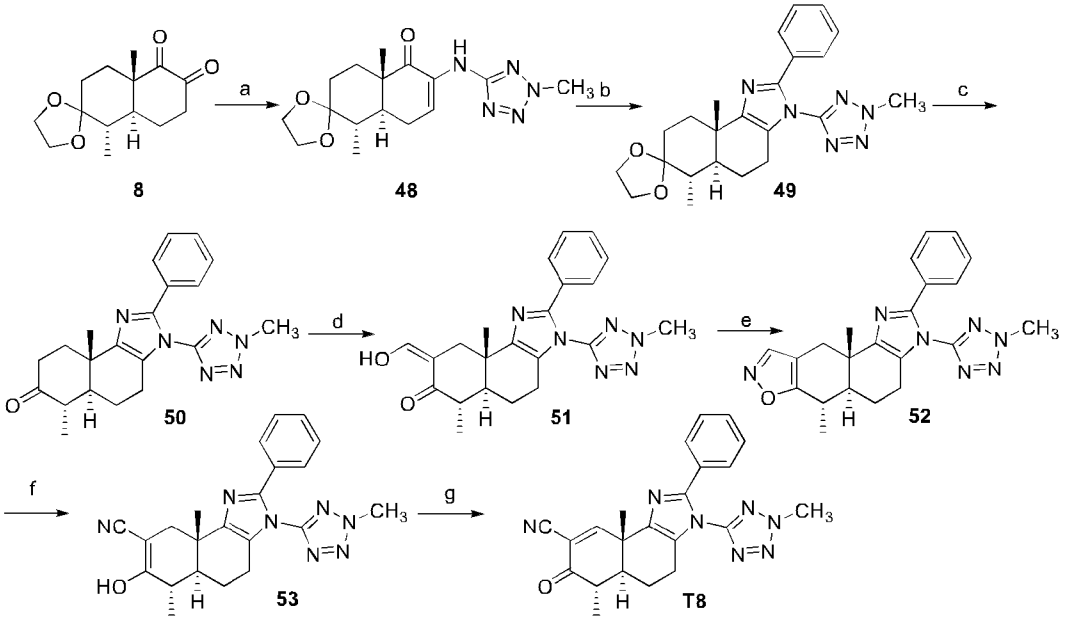
Scheme 8



Reagents and conditions: a) 2-methyl-2*H*-tetrazol-5-amine, $TsOH \cdot H_2O$, benzene, reflux, 63%; b) benzaldehyde, NH_4OAc, EtOH, rt to 50 ºC, 90%; c) aq. HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 50 ºC; f) NaOMe, MeOH, THF, rt, 79% from **49**; g) i) Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 33%.

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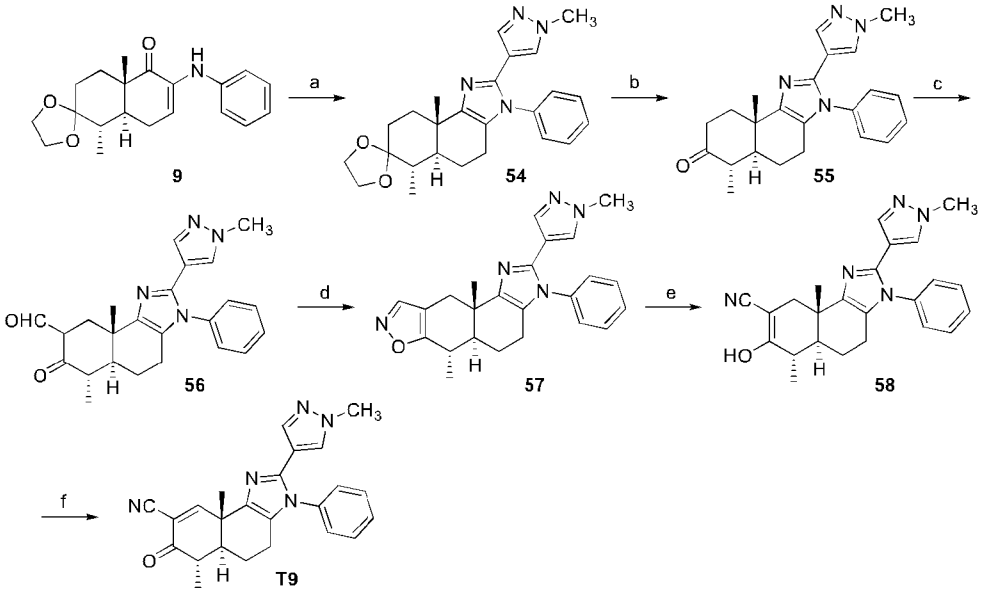
Scheme 9



Reagents and conditions: a) NH_4OAc, 1-methyl-1*H*-pyrazole-4-carbaldehyde, EtOH, rt, 87%: b) aq. HCl, THF, rt, 97%; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH{\cdot}HCl$, EtOH, 50 °C to rt; e) NaOMe, MeOH, THF, rt, 95% from **55**; f) i) DBDMH, DMF, 0 °C; ii) pyridine, 60 °C, 44%.

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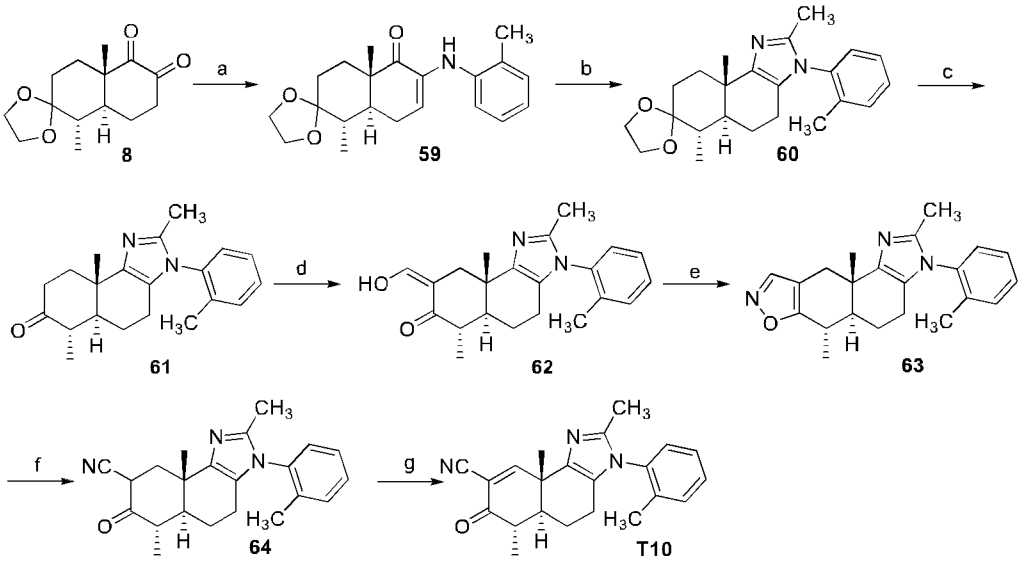
Scheme 10



Reagents and conditions: a) 2-methyl-aniline,$TsOH \cdot H_2O$, benzene, reflux, 53%; b) MeCHO, NH_4OAc, EtOH, rt, 27%; c) aq. HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 50 ºC; f) NaOMe, MeOH, THF, rt, 86% from **60**; g) i) Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 27%.

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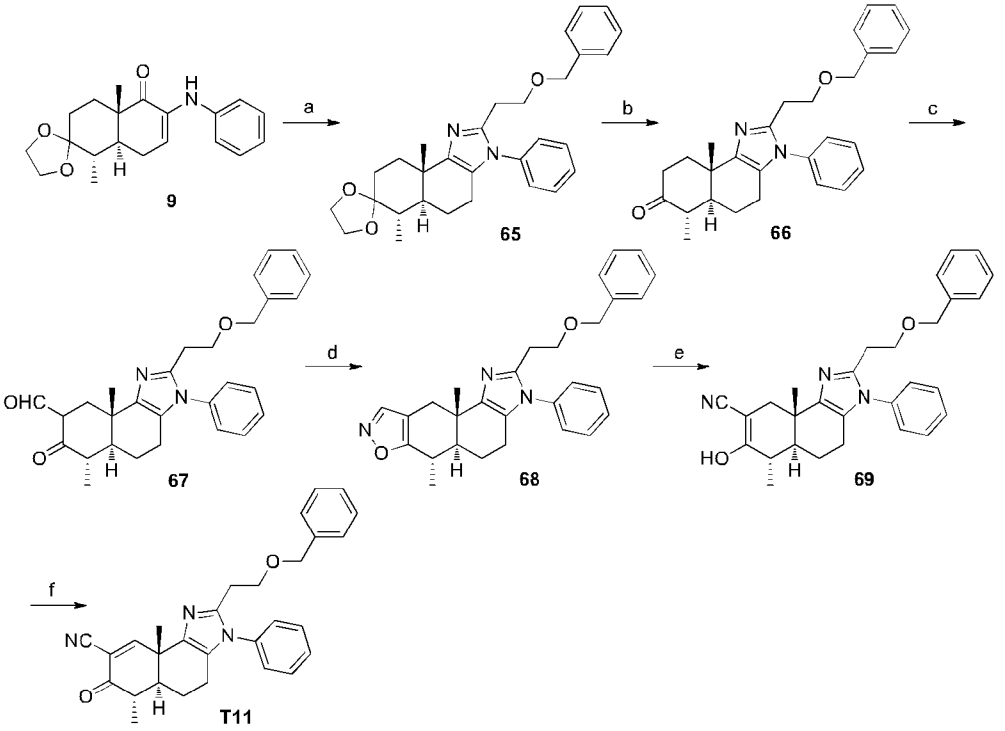
Scheme 11



Reagents and conditions: a) NH_4OAc, 3-(benzyloxy)propanal, EtOH, rt to 80 ºC, 35%: b) aq. HCl, THF, rt, 91%; c) HCO_2Et, NaOMe, MeOH, rt, 99%; d) $NH_2OH \cdot HCl$, EtOH, 50 ºC, 95%; e) NaOMe, MeOH, THF, rt, 76%; f) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 ºC, 52%.

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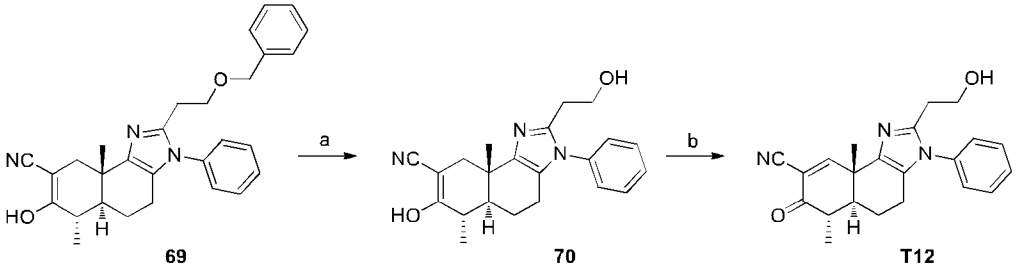
Scheme 12



Reagents and conditions: a) H_2, $Pd(OH)_2/C$, MeOH, rt, 9%; b) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 ºC, 58%.

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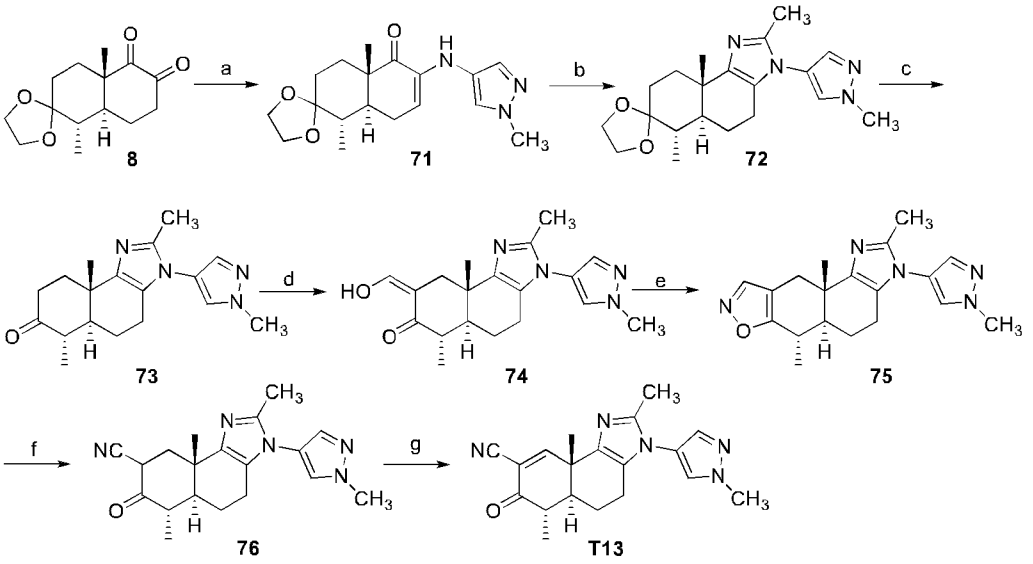
Scheme 13



Reagents and conditions: a) 1-methyl-1*H*-pyrazol-4-amine,$TsOH \cdot H_2O$, benzene, reflux, 79%; b) CH_3CHO, NH_4OAc, EtOH, rt, 93%; c) aq. HCl, THF, rt; d) HCO_2Et, NaOMe, MeOH, rt; e) $NH_2OH \cdot HCl$, EtOH, 50 ºC; f) NaOMe, MeOH, THF, rt, 77% from **72**; g) i) Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 36%.

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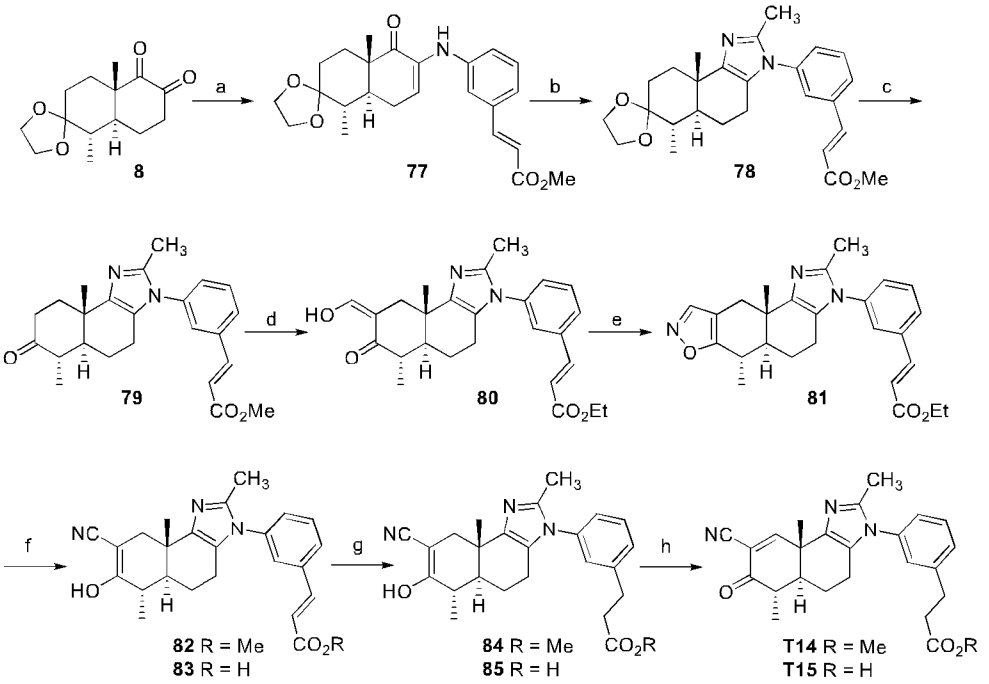
Scheme 14



Reagents and conditions: a) (*E*)-methyl 3-(3-aminophenyl) acrylate ,$TsOH \cdot H_2O$, benzene, reflux, 92%; b) acetaldehyde, NH_4OAc, EtOH, rt, 29%; c) aq. HCl, THF, rt, 90%; d) HCO_2Et, NaOMe, MeOH, rt, 95%; e) $NH_2OH \cdot HCl$, EtOH, 50 °C, 95%; f) NaOMe, THF, rt; g) 10% Pd/C, EtOAc, THF, H_2, 1 atm, rt, **84**: 29% from **81**; **85**: 28% from **81**; h) i) Br_2, DMF/CH_2Cl_2, 0 °C; ii) pyridine, 50 °C, **T14**: 27%; **T15**: 16%.

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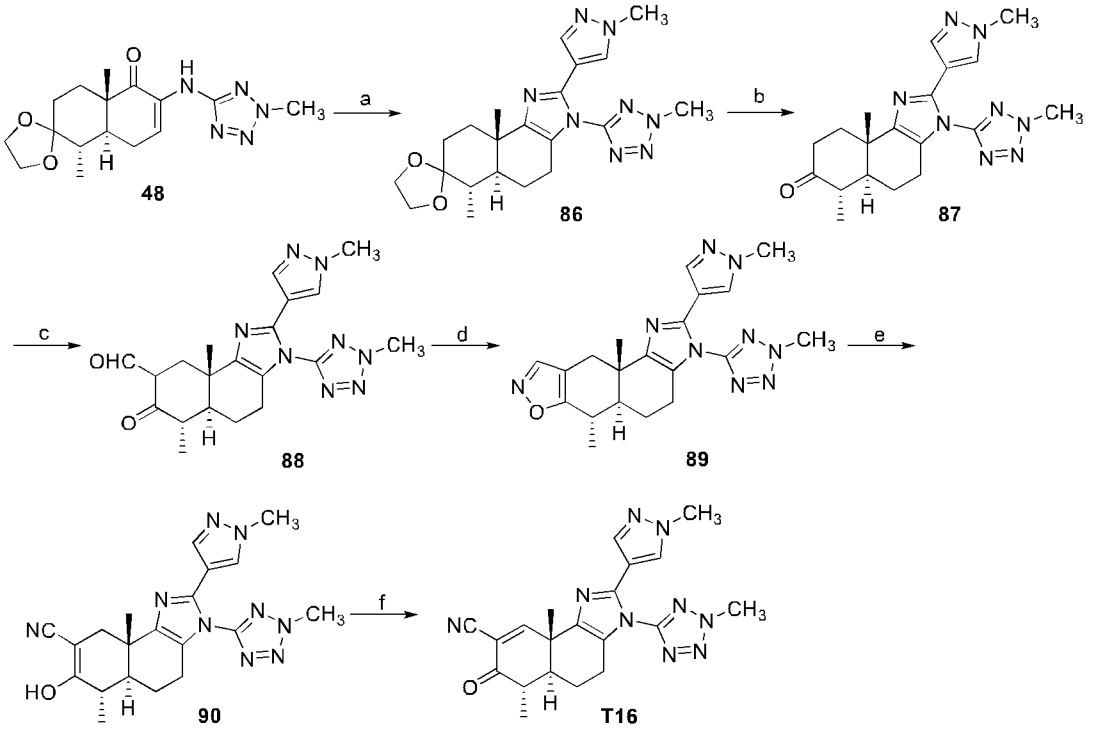
Scheme 15



Reagents and conditions: a) 1-methyl-1*H*-pyrazole-4-carbaldehyde, NH_4OAc, EtOH, THF, rt, 29%; b) aq. HCl, THF, rt, 59%; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH{\cdot}HCl$, EtOH, 50 ºC, 92% from **87**; e) NaOMe, MeOH, THF, rt, 75%; f) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 °C, 37%.

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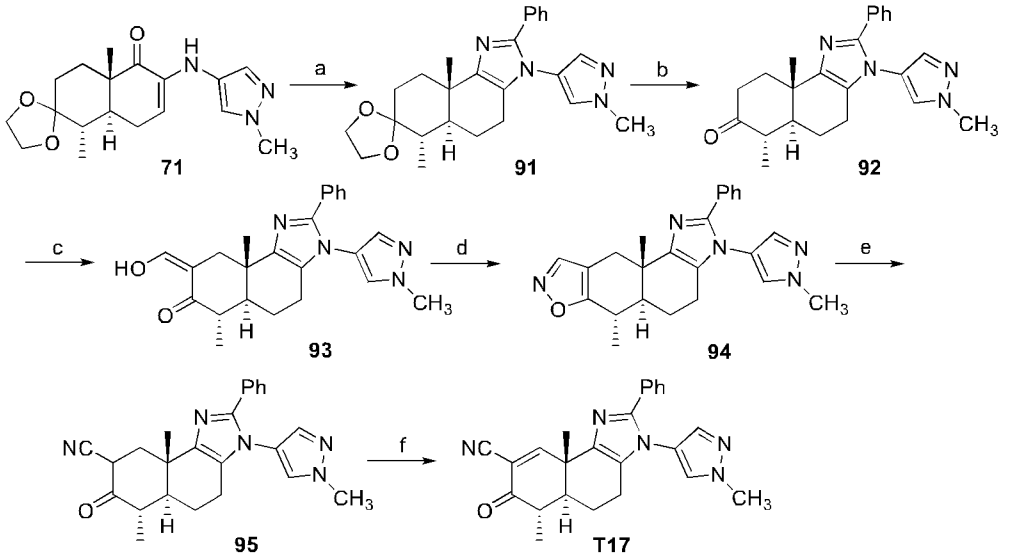
Scheme 16



Reagents and conditions: a) benzaldehyde, NH_4OAc, EtOH, rt, 88%; b) aq. HCl, THF, rt; c) HCO_2Et, NaOMe, MeOH, rt; d) $NH_2OH \cdot HCl$, EtOH, 50 ºC; e) NaOMe, MeOH, THF, rt; f) i) Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 46% from **91**.

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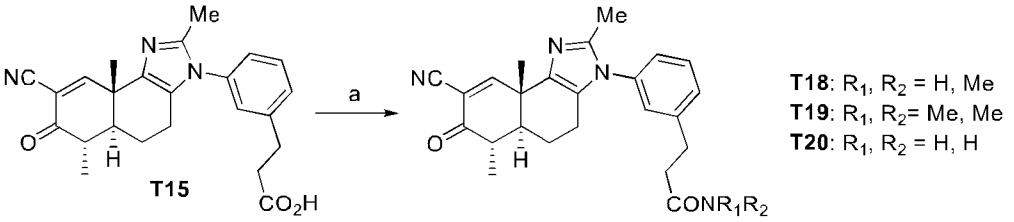
Scheme 17



Reagents and conditions: a) i) Oxalyl chloride, CH_2Cl_2, DMF (cat.), 0 °C; ii) $NHRR_1$, CH_2Cl_2, 0 °C to rt, **T18**: 32%; **T19**: 38%; **T20**: 10%.

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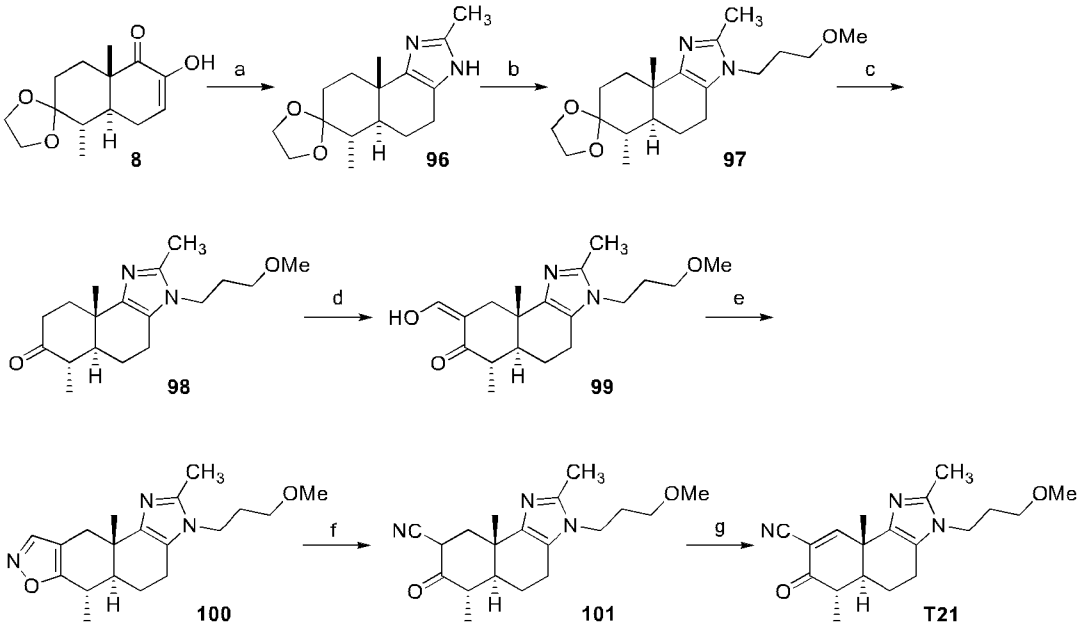
Scheme 18



Reagents and conditions: a) NH_4OAc, CH_3CHO, EtOH, rt, 77%; b) Cs_2CO_3, $Br(CH_2)_3OMe$, MeCN, 85 °C, 92%; c) aq. HCl, THF, rt, 79%; d) HCO_2Et, NaOMe, MeOH, rt, 79%; e) $NH_2OH \cdot HCl$, EtOH, 50 °C, 87%; f) NaOMe, MeOH, THF, rt, 93%; g) i) Br_2, DMF/CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 15%.

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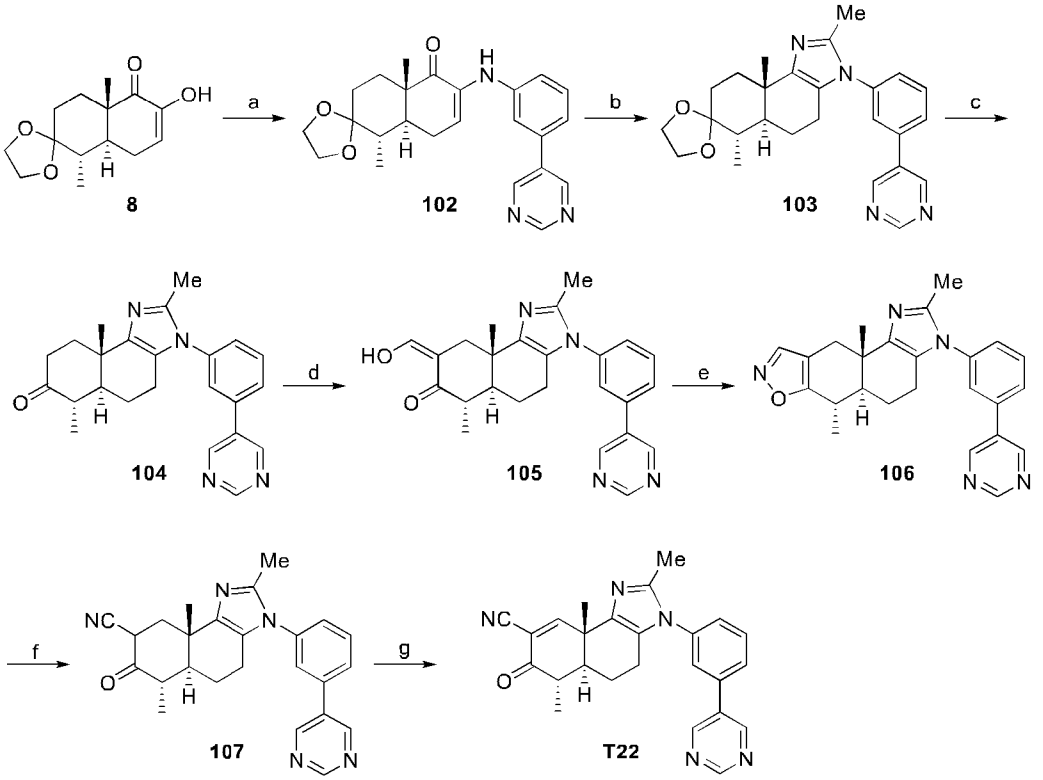
Scheme 19



Reagents and conditions: a) 3-pyrimidin-5-ylaniline, *p*-TsOH·H_2O, benzene, 80 °C, 78%; b) NH_4OAc, CH_3CHO, EtOH, THF, rt, 57%: c) aq. HCl, THF, rt, 99%; d) HCO_2Et, NaOMe, MeOH, THF, rt, 98%; e) NH_2OH·HCl, EtOH, 50 ºC, 65%; f) NaOMe, MeOH, THF, rt, quant.; g) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 ºC, 54%.

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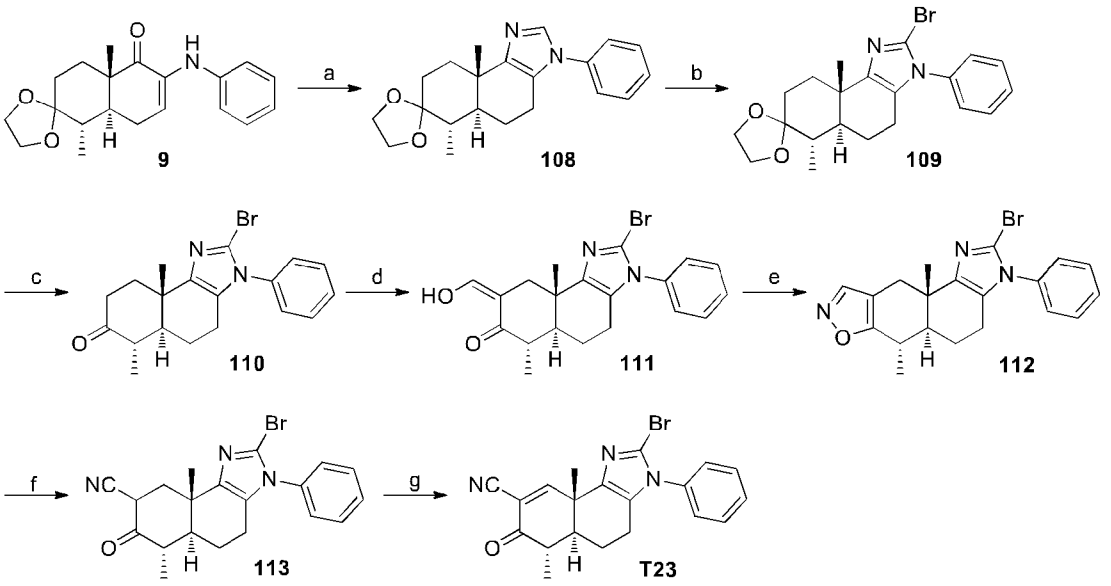
Scheme 20



Reagents and conditions: a) NH_4OAc, aq. HCHO, EtOH, rt, 96%; b) NBS, MeCN, rt, 96%; c) aq. HCl, THF, rt, quant.; d) HCO_2Et, NaOMe, MeOH, rt, 66%; 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, 33% from **111**.

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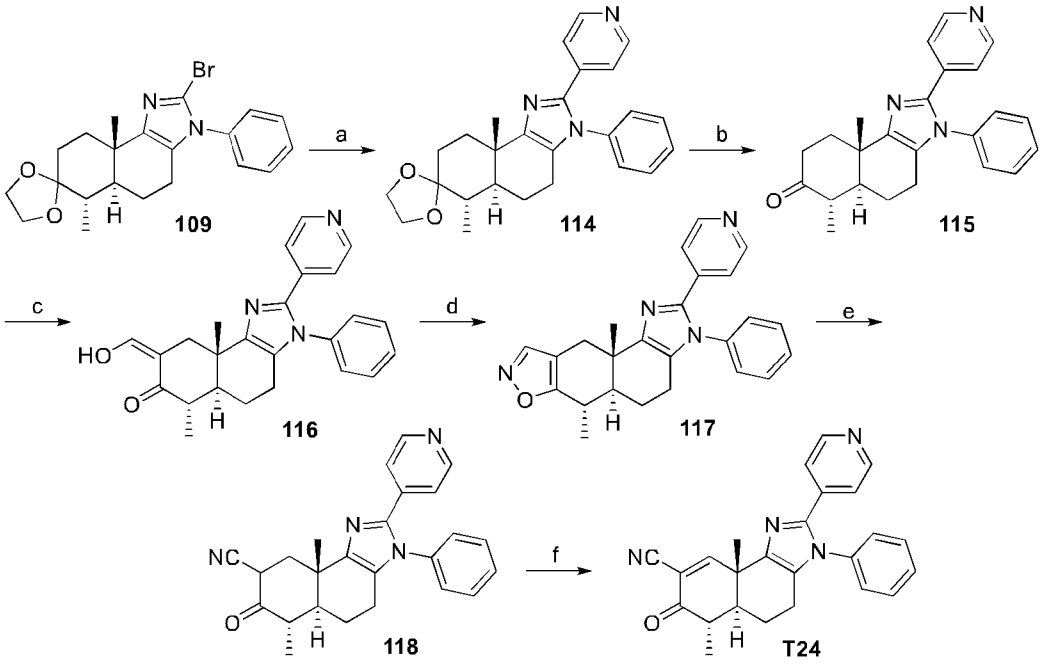
Scheme 21



Reagents and conditions: a) pyridin-4-ylboronic acid, $Pd(dppf)Cl_2$, K_2CO_3, dioxane, DMF, 100 °C, 98%; b) aq. HCl, THF, rt, 70%; c) HCO_2Et, NaOMe, MeOH, rt, 94%; d) $NH_2OH{\cdot}HCl$, EtOH, 50 ºC; e) NaOMe, MeOH, THF, rt; f) i) Br_2, DMF, CH_2Cl_2, 0 ºC; ii) pyridine, 50 ºC, 43% from **116**.

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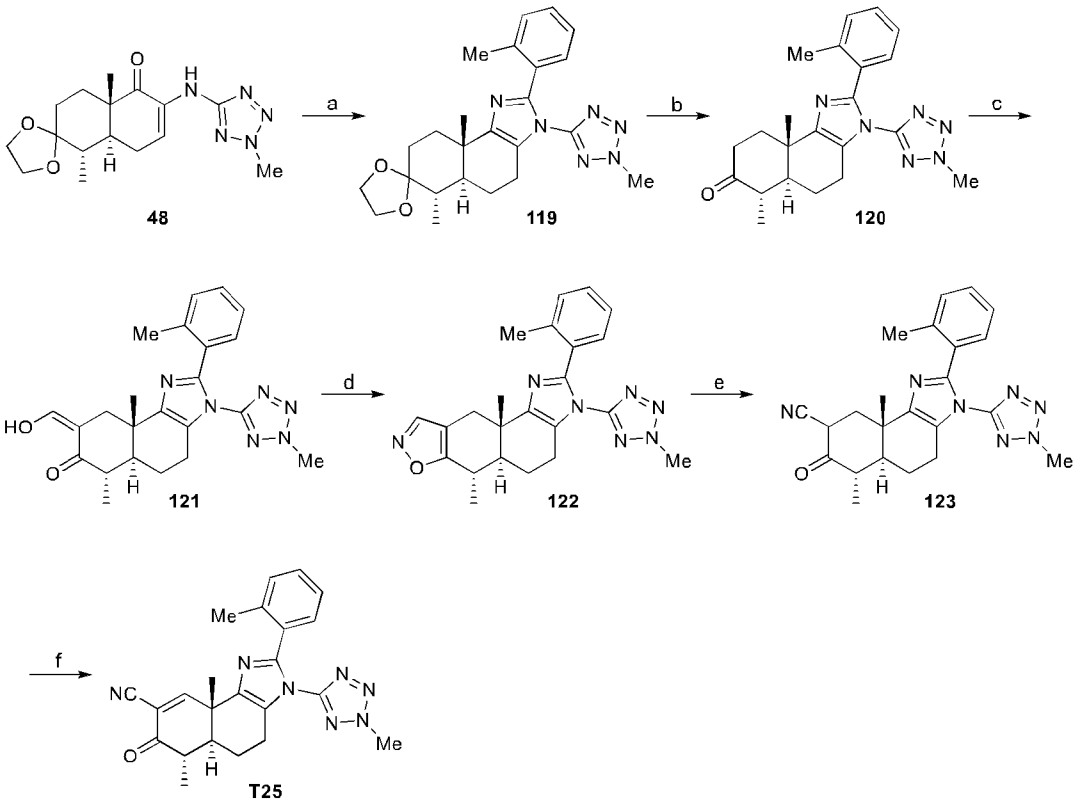
Scheme 22



Reagents and conditions: a) NH_4OAc, *o*-tolualdehyde, THF, EtOH, 80 °C, 83%; b) aq. HCl, THF, rt, quant.; c) HCO_2Et, NaOMe, MeOH, THF, rt, 94%; d) $NH_2OH \cdot HCl$, EtOH, 50 ºC, 42%; e) NaOMe, MeOH, THF, rt; f) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 ºC, 42% from **122**.

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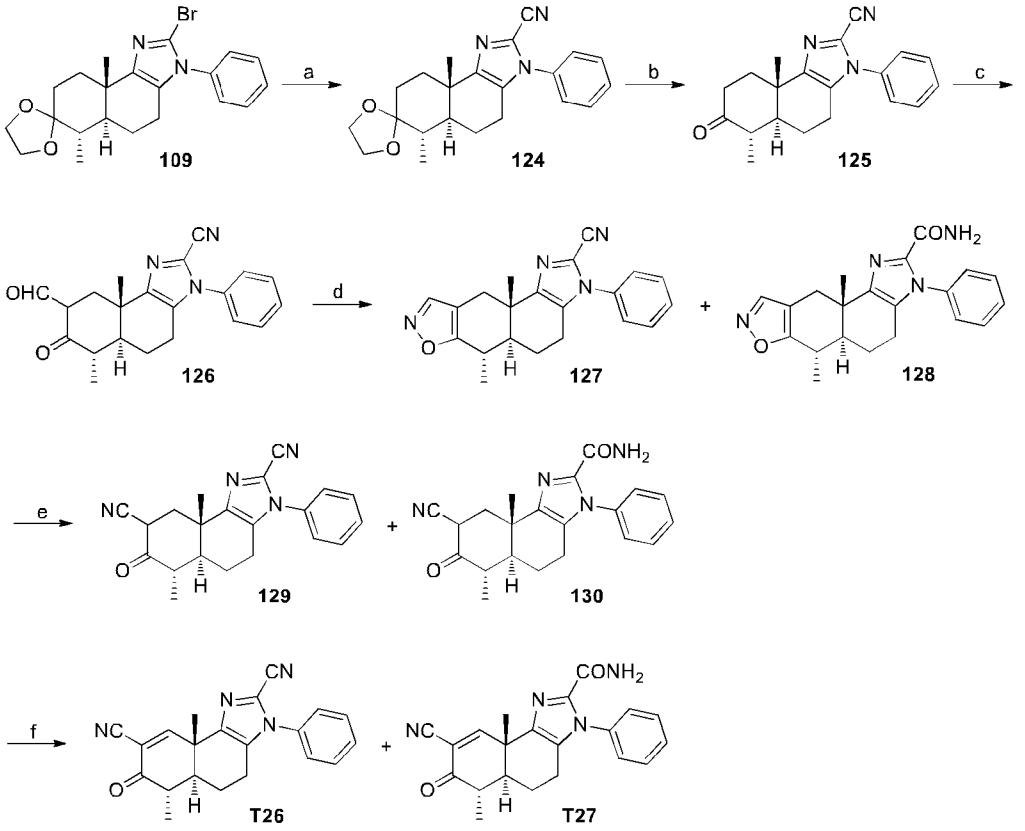
Scheme 23



Reagents and conditions: a) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 180 °C, 88%; b) aq. HCl, THF, MeOH, rt; c) HCO_2Et, NaOMe, MeOH, THF, rt; d) $NH_2OH \cdot HCl$, EtOH, 60 ºC; e) NaOMe, MeOH, rt; f) i) DBDMH, DMF, 0 ºC; ii) pyridine, 60 ºC, **T26**: 16% from **124**; **T27**: 13% from **124**.

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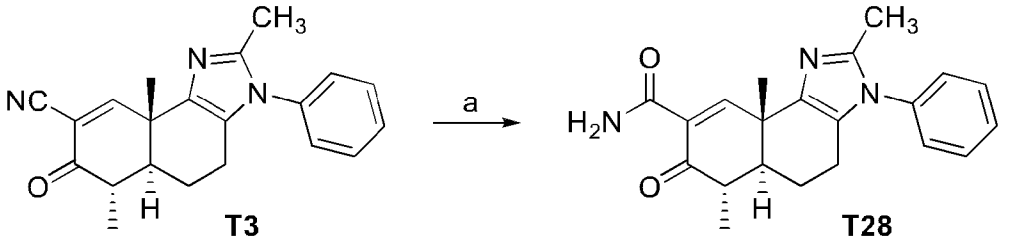
Scheme 24



Reagents and conditions: a) hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II), EtOH, H_2O, 90 °C, 50%.

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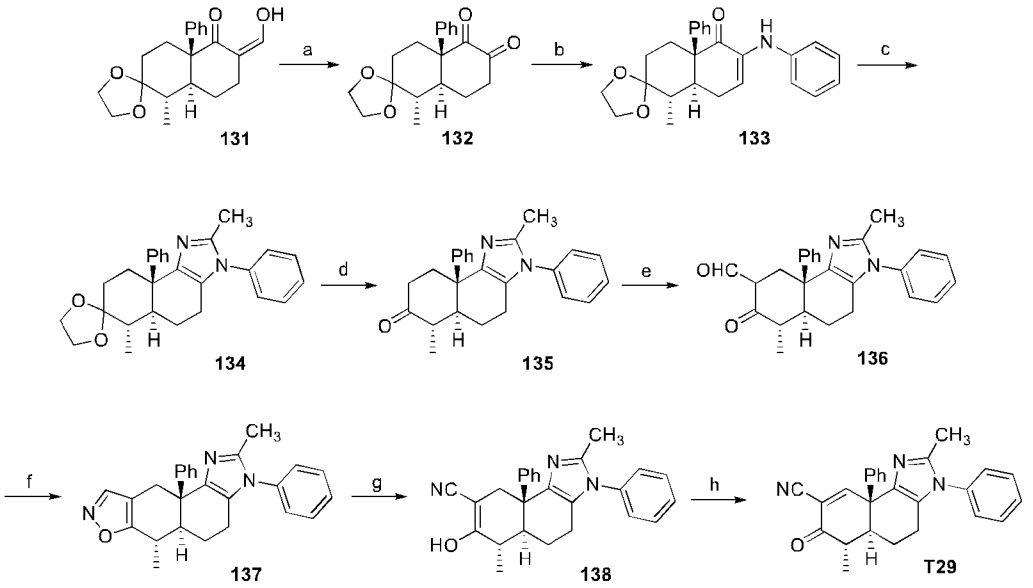
Scheme 25 (Proposed)



Reagents and conditions: a) i) Ozone; ii) Me_2S; b) aniline, $TsOH \cdot H_2O$; c) NH_4OAc, CH_3CHO; d) aq. HCl; e) HCO_2Et, NaOMe; f) $NH_2OH \cdot HCl$; g) NaOMe; h) i) DBDMH; ii) pyridine.

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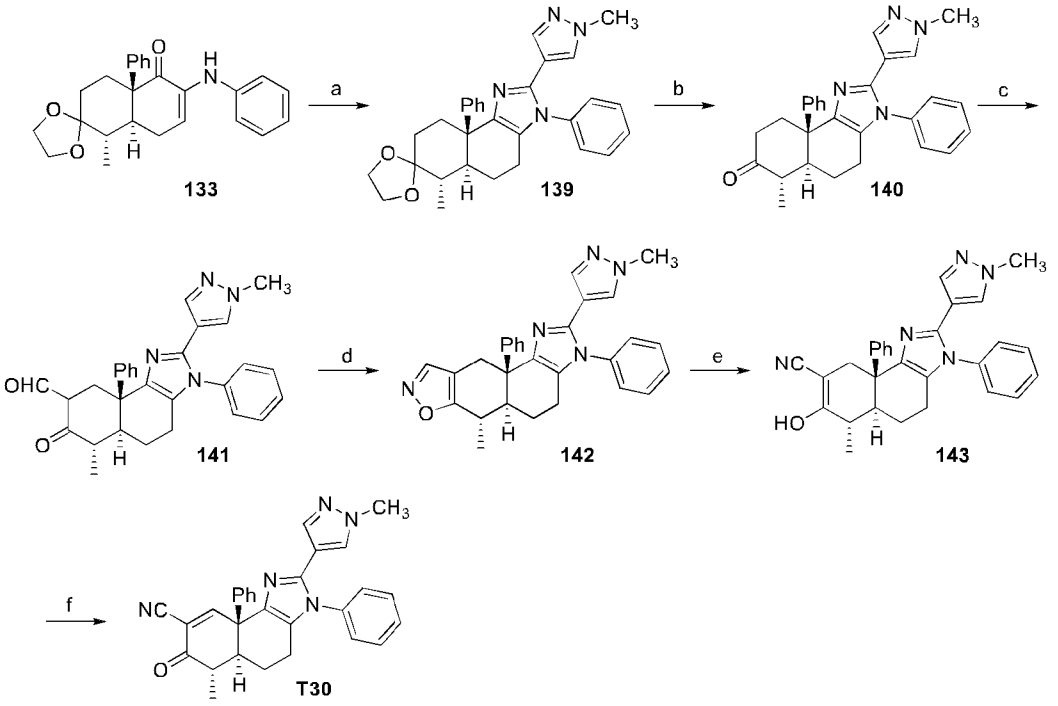
Scheme 26 (Proposed)



Reagents and conditions: a) NH_4OAc, 1-methyl-1*H*-pyrazole-4-carbaldehyde; b) aq. HCl; c) HCO_2Et, NaOMe; d) $NH_2OH \cdot HCl$; e) NaOMe; f) i) DBDMH; ii) pyridine.

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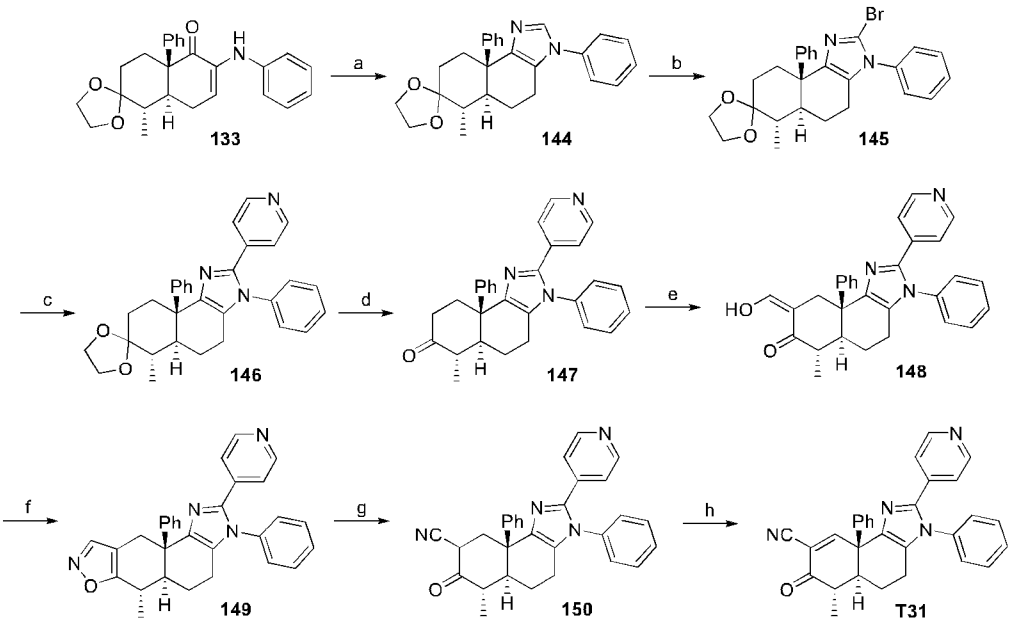
Scheme 27 (Proposed)



Reagents and conditions: a) NH_4OAc, aq. HCHO; b) NBS; c) pyridin-4-ylboronic acid, $Pd(dppf)Cl_2$, K_2CO_3; d) aq. HCl; e) HCO_2Et, NaOMe; f) $NH_2OH \cdot HCl$; g) NaOMe; h) i) DBDMH or Br_2; ii) pyridine

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Compound 2: Compound **1** (500 mg, 2.1 mmol) was dissolved in THF (10 mL), and was cooled to -30 °C. A solution of potassium *tert*-butoxide (293 mg, 2.4 mmol) in THF (10 mL) was added. The reaction was stirred at room temperature for 30 min, and was cooled to -30 °C. Isoamyl nitrite (0.35 mL, 2.6 mmol) was added. The reaction was stirred at room temperature for 16 h. After the solvent was removed, the residue was partitioned between water and *tert*-butyl methyl ether. The aqueous phase was cooled to 0 °C. EtOAc was added. The mixture was adjusted to pH 7 with 1N aq. HCl (1.3 mL, 1.3 mmol). The product was extracted with EtOAc. Organic extract was dried with Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0-50% EtOAc in hexanes) to give compound **2** (330 mg, 59% yield) as a white foam solid.

Compound 3: Compound **2** (198 mg, 0.74 mmol) and benzylamine (98 µL, 0.90 mmol) were mixed in a sealed vial, and heated at 150 °C for 2 h. After cooled to room temperature, the crude was purified by column chromatography (silica gel, 0-25% acetone in hexanes) to give compound **3** (94 mg, 38% yield) as a yellow foam solid. *m/z* = 339.2 (M+1).

Compound 4: A mixture of compound **3** (100 mg, 0.30 mmol), *p*-toluenesulfonic acid monohydrate (337 mg, 1.77 mmol), acetone (3 mL) and water (0.6 mL) were stirred at room temperature for 3 h. EtOAc was added. The mixture was treated with aq. $NaHCO_3$ to pH > 7, and was transferred to a separatory funnel. The organic extract was separated, washed with water, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (silica gel, 0-25% acetone in hexanes) to give compound **4** (90 mg, 100% yield) as a yellow foam solid. *m/z* = 295.1 (M+1).

Compound 5: NaOMe (25 wt. % in methanol, 230 µL, 1.00 mmol) was added to a mixture of compound **4** (20 mg, 68 µmol) in HCO_2Et (160 µL, 1.99 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction was cooled to 0 °C. MTBE and 6 N aq. HCl (170 µL, 1.02 mmol) were added sequentially. The mixture was treated with aq. $NaHCO_3$ to pH ~ 6.7. The product was extracted with EtOAc. Combined organic extracts were dried with Na_2SO_4, filtered and concentrated.

The residue was mixed with $NH_2OH{\cdot}HCl$ (7 mg, 100 µmol), EtOH (1 mL) and water (0.1 mL). After heated at 55 °C for 1 h, 1 N aq. HCl (100 µL, 100 µmol) was added. The reaction was heated for an additional 18 h. EtOH was removed. EtOAc was added. The mixture was treated with aq. $NaHCO_3$ to pH > 7. Product was

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extracted with EtOAc. Combined organic extracts were washed with water, dried with Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (silica gel, 0-50% EtOAc in hexanes) to give compound **5** (15 mg, 69% yield) as a white foam solid. *m/z* = 320.1 (M+1).

Compound 6: NaOMe (16 µL, 69.3 µmol) was added to a solution of compound **5** (15 mg, 46.9 µmol) in MeOH (470 µL) at room temperature. After the reaction was heated at 55 °C for 1 h, MTBE (200 mL) was added. The mixture was treated with 1 N aq. HCl to pH ~ 7. Product was extracted with EtOAc. Combined organic extracts were washed with water, dried with Na_2SO_4, filtered and concentrated to give compound **6** (13 mg, 87% yield) as a white solid. *m/z* = 320.1 (M+1).

Compound T1: A solution of 1,3-dibromo-5,5-dimethylhydantoin (6.2 mg, 21.7 µmol) in DMF (110 µL) was added to a solution of compound **6** (13.8 mg, 43.1 µmol) in DMF (110 µL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (11 µL, 136.3 µmol) was added. The mixture was heated at 55 °C for 2 h. EtOAc was added. The mixture was washed with aq. $NaHCO_3$ and water. Organic extract was washed with water, dried with Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (silica gel, 0-30% acetone in hexanes) to give compound **T1** (11 mg, 80% yield) as light brown foam solid. *m/z* = 318 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (bs, 1H), 8.62 (s, 1H), 7.75 (m, 2H), 7.42 (m, 2H), 7.34 (m, 1H), 2.68-2.82 (m, 2H), 2.55 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.06-2.20 (m, 2H), 1.83 (m, 1H), 1,44 (s, 3H), 1.29 (d, 3H, *J* = 7.2 Hz).

Compound 8: Ozone was bubbled through a stirring solution of compound **7** (2.00 g, 7.15 mmol) in dichloromethane (100 mL) at -78 ºC. The color never turned blue, but TLC after 1.5 h of the light green solution showed no starting material left. Oxygen was bubbled through the solution for 10 min, methyl sulfide (2.8 mL, 38.1 mmol) was added, the dry ice-acetone bath was removed and the sample was stirred at room temperature overnight. The sample was concentrated then chromatographed (silica gel, 30% EtOAc in hexanes) to give compound **8** (1.86 g, 98% yield) as a light yellow solid. *m/z* = 253 (M+1).

Compound 9: Compound **8** (1.04 g, 4.12 mmol) was taken up in benzene (200 mL). Aniline (1.2 g, 12.4 mmol) and *p*-toluenesulfonic acid monohydrate (780 mg, 4.12 mmol) were added. The reaction was stirred at refluxing for 16 h. The reaction mixture was filtered, concentrated. The crude residue was purified by column

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chromatography (silica gel, 0 to 20% EtOAc in hexanes) to give compound **9** (0.8 g, 60% yield) as an oil. *m/z* = 328 (M+1).

Compound 10: Compound **9** (740 mg, 2.26 mmol) was dissolved in EtOH (50 mL). Benzaldehyde (480 mg, 4.52 mmol) and ammonium acetate (1.75 g, 22.6 mmol) were added. The reaction mixture was stirred for two days at room temperature. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 35% EtOAc in hexanes) to give compound **10** (800 mg, 85% yield) as an off-white solid. *m/z* = 415 (M+1).

Compound 11: Compound **10** (800 mg, 1.93 mmol) was taken up in THF (10 mL), and 3N HCl (aq, 5 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and was extracted with ethyl acetate. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give a solid compound **11** (720 mg, quantitative yield). *m/z* = 371 (M+1).

Compound 12: Compound **11** (720 mg, 1.93 mmol) was taken up in ethyl formate (15 mL, 187.5 mmol). NaOMe (30 wt. % in methanol, 1.4 g, 5.8 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 compound **12** (770 mg, quantitative yield) as a solid. *m/z* = 399 (M+1).

Compound 13: Compound **12** (770 mg, 1.93 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (270 mg, 3.86 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 ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **13** (765 mg, quantitative yield) as a solid. *m/z* = 396 (M+1).

Compound 14: Compound **13** (765 mg, 1.93 mmol) was dissolved in THF (5 mL), and NaOMe (30 wt. % in methanol, 1.5 g, 7.72 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **14** (600 mg, 78% yield) as a solid. *m/z* = 396 (M+1).

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Compound T2: Compound **14** (205 mg, 0.51 mmol) was dissolved in dry DMF (3 mL), and the solution was cooled to 0 °C. Bromine (91 mg in 1 mL of dichloromethane, 0.57 mmol) was added, and the reaction was stirred at 0 °C for 2 h. Pyridine (1 mL, 13 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 35% EtOAc in hexanes) to give compound **T2** (60 mg, 30% yield) as an off-white solid. *m/z* = 394 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.43 (dd, 2H, *J* = 1.9, 5.0 Hz), 7.43 (m, 1H), 7.34 (m, 2H), 7.20 (m, 5H), 2.59 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.51 (m, 2H), 2.16 (dt, 1H, *J* = 2.2, 12.8 Hz), 2.06 (m, 1H), 1.82 (m, 1H), 1.53 (s, 3H), 1.30 (d, 3H, *J* = 6.8 Hz);

Compound 15: In a sealable vial, a mixture of **9** (0.82 g, 2.50 mmol), ammonium acetate (1.92 g, 25.04 mmol) and acetaldehyde (0.28 mL, 5.00 mmol) in ethanol (10 mL) was flushed with N_2, sealed and stirred at room temperature. TLC (silica gel, 30% EtOAc in hexanes) after 16 h at room temperature still showed starting material (R_f 0.42) present. Another portion of acetaldehyde (0.28 mL, 5.00 mmol) was added. The sample was again flushed with N_2, sealed and stirred at room temperature for 48 h. The sample was concentrated then partitioned between 10% aq. NH_4OH solution (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), filtered, concentrated and chromatographed (silica gel, 10% methanol in EtOAc) to give compound **15** (0.70 g, 80% yield) as tan solid. *m/z* = 353 (M+1, 100%).

Compound 16: A solution of **15** (0.70 g, 2.00 mmol) and 1N aq. HCl (20 mL, 20 mmol) in methanol (50 mL) was stirred at room temperature under N_2 for 16 h. The sample was concentrated, cooled, basified with 10% aq. NH_4OH solution (to pH ~ 9-10) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extract was dried ($MgSO_4$), filtered and concentrated to give compound **16** (0.59 g, 96% yield) as off-white solid, which was used in the next step without purification. *m/z* = 309 (M+1, 100%).

Compound 17: To a stirring solution at room temperature under N_2 of compound **16** (0.59 g, 1.91 mmol) and ethyl formate (15.5 mL, 191.9 mmol) in benzene (25 mL) was added sodium methoxide (30 wt. % solution in methanol, 1.8 mL, 9.6 mmol). After 16 h, the solution was concentrated, cooled, acidified with excess saturated KH_2PO_4 solution (50 mL) and extracted with $CHCl_3$ (3 × 25 mL).

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The combined organic extract was dried ($MgSO_4$), filtered and concentrated to give compound **17** (0.80 g, quantitative yield) as tan foamy solid, which was used in the next reaction without purification. *m/z* = 337 (M+1).

Compound 18: A stirring solution under N_2 of sl. impure compound **17** (entire amount from last step, ≤ 1.91 mmol) and hydroxylamine hydrochloride (0.20 g, 2.88 mmol) in ethanol (25 mL) was heated at 50 °C for 2 h then room temperature overnight. The solution was concentrated, cooled, basified with saturated $NaHCO_3$ solution (50 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extract was dried ($MgSO_4$), filtered and concentrated to give compound **18** (0.76 g, quantitative yield) as tan foamy solid, which was used in the next reaction without purification. *m/z* = 334 (M+1).

Compound 19: To a stirring solution at room temperature under N_2 of compound **18** (from last step [entire amount, used without purification], ≤ 1.91 mmol) in methanol (20 mL) was added sodium methoxide (30 wt. % solution in methanol, 1.8 mL, 9.6 mmol). The sample was stirred at room temperature for 16 h, concentrated, cooled, acidified with excess saturated KH_2PO_4 solution (50 mL) and extracted with $CHCl_3$ (3 × 25 mL). The combined organic extract was dried ($MgSO_4$), filtered and concentrated to give compound **19** (0.70 g, quantitative yield) as tan foamy solid, which was used in the next reaction without purification. *m/z* = 334 (M+1, 100%).

Compound T3: To a stirring solution at ~0 °C under N_2 of compound **19** (entire amount from last step, ≤ 1.91 mmol) in DMF (5 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.27 g, 0.94 mmol) in DMF (5 mL). After stirring at 0 °C for 30 min, pyridine (1.5 mL, 18.5 mmol) was added. The ice-bath was removed, the sample was heated at 50 °C for 4 h, cooled, concentrated then partitioned between saturated KH_2PO_4 solution (50 mL) and $CHCl_3$ (50 mL). The aqueous extract was extracted with fresh $CHCl_3$ (2 × 25 mL). The combined organic extract was dried ($MgSO_4$), filtered, concentrated and chromatographed (silica gel, 100% EtOAc) to give compound **T3** (0.18 g, 28% yield from **16**) as off-white solid. *m/z* = 332 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.49 (m, 3H), 7.21 (m, 2H), 2.55 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.45 (ddd, 1H, *J* = 6.4, 11.0, 17.3 Hz), 2.37 (dd, 1H, *J* = 6.6, 16.6 Hz), 2.26 (s, 3H), 2.11 (dt, 1H, *J* = 2.3, 12.8 Hz), 2.02 (m, 1H), 1.74 (tdd, 1H, *J* = 6.5, 11.2, 13.3 Hz), 1.45 (s, 3H), 1.28 (d, 3H, *J* = 6.8 Hz).

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Compound 20: Compound **8** (1.21 g, 4.8 mmol) was taken up in benzene (200 mL). 3-Bromoaniline (2.45 g, 14.4 mmol) and $TsOH \cdot H_2O$ (125 mg, 0.5 mmol) were added. The reaction was stirred at refluxing for 16 h. The reaction mixture was filtered, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 25% EtOAc in hexanes) to give compound **20** (1.4 g, 72% yield) as an oil. *m/z* = 406, 408 (1:1, M+1).

Compound 21: Compound **20** (445 mg, 1.1 mmol) was dissolved in EtOH (20 mL). Benzaldehyde (235 mg, 2.2 mmol) and ammonium acetate (0.85g, 11 mmol) were added. The reaction mixture was stirred for 24 h at room temperature, and then heated at 65 °C for two days. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 35% EtOAc in hexanes) to give compound **21** (420 mg, 77% yield) as an off-white solid. *m/z* = 493, 495 (1:1, M+1)..

Compound 22: Compound **21** (175 mg, 0.35 mmol) was taken up in toluene/Et_3N (4:1, 5 mL). CuI (10 mg, 0.05 mmol), $Pd(PPh_3)_2Cl_2$ (20 mg, 0.03 mmol) and propargyl alcohol (25 mg, 0.44 mmol) were added. The mixture was bubbled with N_2 for 10 min. The reaction was stirred at 80 °C for 16 h. The reaction mixture was filtered, concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 75% EtOAc in hexanes) to give compound **22** (150 mg, 30% yield) as a solid. *m/z* = 469 (M+1).

Compound 23: Compound **22** (125 mg, 0.267 mmol) was hydrogenated at atmospheric pressure in EtOAc (15 mL) over 10% Pd/C (25 mg) for 16 h at room temperature. The reaction mixture was filtered using a Celite® pad. The filtrate was concentrated to give compound **23** (82 mg, 67% yield) as an oil. *m/z* = 473 (M+1).

Compound 24: Compound **23** (82 mg, 0.17 mmol) was taken up in THF (2 mL), and 3N HCl (aq, 1 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give compound **24** (70 mg, 96% yield) as a foam. *m/z* = 429 (M+1).

Compound 25: Compound **24** (70 mg, 0.16 mmol) was taken up in ethyl formate (10 mL, 125 mmol). NaOMe (30 wt. % in methanol, 120 mg, 0.65 mmol) was added. The mixture was stirred at room temperature overnight. The reaction

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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 **25** (70 mg, 96% yield) as an oil. *m/z* = 457 (M+1).

Compound 26: Compound **25** (70 mg, 0.15 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (35 mg, 0.5 mmol) was added. The reaction mixture was stirred overnight at 50 ºC. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **26** (65 mg, 96% yield) as an oil. *m/z* = 454 (M+1).

Compound 27: Compound **26** (65 mg, 0.14 mmol) was dissolved in THF (2 mL), and NaOMe (30 wt. % in methanol, 105 mg, 0.56 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **27** (65 mg, 94% yield) as an oil. *m/z* = 496 (M+1).

Compound T4: Compound **27** (65 mg, 0.14 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Br_2 (25 mg in 1 mL of dichloromethane, 1.1 eq)) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (1 mL, 13 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 55% EtOAc in hexanes) to give compound **T4** (10 mg, 15% yield) as an off-white solid. *m/z* = 494 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.34 (m, 3H), 7.23 (m, 4H), 7.01 (m, 2H), 3.98 (t, 2H, *J* = 6.5 Hz), 2.67 (t, 2H, 7.6 Hz), 2.56 (m, 3H), 2.12 (m, 2H), 2.04 (s, 3H), 1.86 (m, 3H), 1.52 (s, 3H), 1.30 (d, 3H, *J* = 6.8 Hz).

Compound 28: Compound **8** (270 mg, 1.07 mmol) was taken up in benzene (10 mL), and biphenyl-4-amine (199 mg, 1.18 mmol) was added followed by *p*-TsOH·H_2O (10 mg). The solution was heated at 80 °C for 2 days. The mixture was cooled, diluted with saturated $NaHCO_3$ (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 0.44 g of a dark foam. Flash chromatography (silica gel, 100% CH_2Cl_2) gave compound **28** (270 mg, 62% yield) as an orange-yellow foam. *m/z* = 404 (M + 1).

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Compound 29: Compound **28** (260 mg, 0.64 mmol) was suspended in THF (2 mL) and EtOH (2 mL). Ammonium acetate (497 mg, 6.44 mmol) was added followed by acetaldehyde (0.14 mL, 2.49 mmol). The mixture was stirred overnight at room temperature. Another portion of acetaldehyde (0.14 mL) was added, and stirring was continued for another 2 d. The mixture was concentrated, diluted with saturated $NaHCO_3$ (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to give 318 mg of an orange-yellow foam. Flash chromatography (silica gel, 9:1 EtOAc/CH_2Cl_2 then 5% MeOH/EtOAc) gave compound **29** (210 mg, 76% yield) as a light yellow foam. *m/z* = 429 (M + 1).

Compound 30: Compound **29** (210 mg, 0.49 mmol) was taken up in THF (5 mL) and 1M aq. HCl (1 mL) was added. The solution was stirred for 3 d, then diluted with saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **30** (198 mg, quantitative yield) as a light yellow foam. *m/z* = 385 (M + 1).

Compound 31: Compound **30** (0.49 mmol) was taken up in ethyl formate (5 mL) and cooled in an ice bath. NaOMe (0.88 g, 30 wt. % in MeOH) was added dropwise, and the solution was allowed to warm to room temperature and stirred overnight. The mixture was cooled in an ice bath, quenched by the addition of saturated aq. KH_2PO_4 (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **31** (210 mg, quantitative yield) as a light yellow foam. *m/z* = 413 (M+1).

Compound 32: Compound **31** (0.49 mmol) was taken up in EtOH (5 mL). Hydroxylamine hydrochloride (68 mg, 0.98 mmol) was added and the mixture was heated at 50 °C for 3 h, then allowed to cool to room temperature and stirred overnight. The solution was concentrated, diluted with saturated aq. $NaHCO_3$ (25 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **32** (210 mg, quantitative yield) as a light yellow foam. *m/z* = 410 (M+1).

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Compound 33: Compound **32** (0.49 mmol) was taken up in THF (6 mL) and MeOH (2 mL) and NaOMe (0.88 g, 30 wt. % in MeOH) was added. The solution was stirred overnight at room temperature and then concentrated. Saturated aq. KH_2PO_4 (25 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to give 198 mg of a light yellow solid. Flash chromatography (3% MeOH/$CHCl_3$) gave compound **33** (152 mg, 76% yield from **29**) as a light yellow solid. *m/z* = 410 (M + 1).

Compound T5: Compound **33** (150 mg, 0.37 mmol) was taken up in DMF (4 mL) and cooled in an ice bath. N,N′-dibromodimethylhydantoin (63 mg, 0.22 mmol) was added and the solution was stirred 1 h at 0 °C. Pyridine (0.4 mL) was added and the solution was heated at 60 ºC for 3 h. After cooling, the solution was diluted with saturated aq. $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 50 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated, and dried under vacuum to give 150 mg of a brown oil. Flash chromatography (2% MeOH/$CHCl_3$) gave compound **T5** (85 mg, 57% yield) as a light yellow foam. *m/z* = 408 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.71 (m, 2H), 7.62 (m, 2H), 7.49 (m, 2H), 7.42 (m, 1H), 7.28 (m, 2H), 2.57 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.46 (m, 2H), 2.32 (s, 3H), 2.12 (dt, 1H, *J* = 2.2, 12.8 Hz), 2.04 (m, 1H), 1.76 (tdd, 1H, *J* = 6.6, 10.9, 13.2 Hz), 1.46 (s, 3H), 1.29 (d, 3H, *J* = 6.8 Hz).

Compound 34: Compound **20** (1.83 g, 4.5 mmol) was taken up in acetic anhydride (10 g, 100 mmol). NaOAc (1.8 g, 22.5 mmol) was added. The reaction was stirred at 140 ºC for 16 h. The reaction mixture was filtered, concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to give compound **34** (0.7 g, 35% yield) as an oil. *m/z* = 448, 450 (1:1, M+1).

Compound 35: Compound **34** (700 mg, 0.35 mmol) was taken up in DME/Et_3N (4:1, 5 mL). CuI (30 mg, 0.15 mmol), $Pd(PPh_3)_2Cl_2$ (50 mg, 0.08 mmol) and propargyl alcohol (105 mg, 1.88 mmol) were added. The mixture was bubbled with N_2 for 15 min. The reaction was stirred at 80 °C for 16 h. The reaction mixture was filtered, concentrated. The crude residue was purified by column chromatography (silica gel, 25 to 75% EtOAc in hexanes) to give compound **35** (220 mg, 34% yield) as a foam. *m/z* = 424 (M+1).

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Compound 36: Compound **35** (200 mg, 0.47 mmol) was hydrogenated at atmospheric pressure in EtOAc (15 mL) over 10% Pd/C (25 mg) for 16 h at room temperature. The reaction mixture was filtered using a Celite® pad. The filtrate was concentrated to give compound **36** (180 mg, 90% yield) as an oil. *m/z* = 430 (M+1).

Compound 37: Compound **36** (180 mg, 0.42 mmol) was dissolved in EtOH (6 mL). Ammonium acetate (5 g, 65 mmol) was added. The reaction mixture was stirred for 6 h at 90 ºC. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 25 to 100% EtOAc in hexanes) to give compound **37** (67 mg, 39% yield) as a foam. *m/z* = 411 (M+1).

Compound 38: Compound **37** (67 mg, 0.16 mmol) was taken up in THF (1 mL), and 3 N HCl (aq, 1 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give compound **38** (60 mg, quantitative yield) as a foam. *m/z* = 367 (M+1).

Compound 39: Compound **38** (60 mg, 0.16 mmol) was taken up in ethyl formate (10 mL, 125 mmol). NaOMe (30 wt. % in methanol, 120 mg, 0.65 mmol) was added. The mixture was stirred overnight at room temperature. The reaction mixture was neutralized with aq. KH_2PO_4, and was extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **39** (50 mg, 82% yield) as an oil. *m/z* = 395 (M+1).

Compound 40: Compound **39** (50 mg, 0.13 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (30 mg, 0.4 mmol) was added. The reaction mixture was stirred overnight at 50 ºC. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **40** (50 mg, quantitative yield) an oil. *m/z* = 392 (M+1).

Compound 41: Compound **40** (50 mg, 0.13 mmol) was dissolved in THF (2 mL), and NaOMe (30 wt. % in methanol, 95 mg, 0.52 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The

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organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **41** (40 mg, 80% yield) as an oil. *m/z* = 392 (M+1).

Compound T6: Compound **41** (40 mg, 0.1 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Br_2 (18 mg in 1 ml of dichloromethane, 1.1eq) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (1 mL, 13 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 25 to 100% EtOAc in hexanes) to give compound **T6** (10 mg, 25% yield) as a foam. *m/z* = 390 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.42 (m, 1H), 7.05 (m, 3H), 3.71 (t, 2H, *J* = 6.8 Hz), 2.79 (t, 2H, *J* = 7.9 Hz), 2.27 (s, 3H), 2.21 (m, 9H), 1.45 (s, 3H), 1.28 (d, 3H, *J* = 6.7 Hz).

Compound 42: Compound **8** (309 mg, 1.22 mmol) was taken up in benzene (15 mL), and biphenyl-3-amine (228 mg, 1.35 mmol) was added followed by p-toluenesulfonic acid (10 mg). The solution was heated at 80 °C for 2 days then allowed to cool to room temperature and stirred overnight. Saturated $NaHCO_3$ (25 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 0.54 g of a dark foam. Flash chromatography (silica gel, 100% CH_2Cl_2) gave compound **42** (370 mg, 75% yield) as a light orange-yellow foam. *m/z* = 404 (M + 1).

Compound 43: Compound **42** (365 mg, 0.90 mmol) was suspended in THF (3 mL) and EtOH (2 mL). Ammonium acetate (700 mg, 9.0 mmol) was added followed by acetaldehyde (0.20 mL, 3.62 mmol). The mixture was stirred overnight at room temperature. Another portion of acetaldehyde (0.20 mL) was added, and stirring was continued for another 2 d. The mixture was concentrated, diluted with saturated $NaHCO_3$ (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to give 0.42 g of an orange-yellow foam. Flash chromatography (silica gel, 3% MeOH/EtOAc) gave of compound 43 (288 mg, 74% yield) as a light yellow foam. *m/z* = 429 (M + 1).

Compound 44: Compound **43** (288 mg, 0.67 mmol) was taken up in THF (5 mL) and 1M HCl (1 mL) was added. The solution was stirred for 3 d. Saturated

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$NaHCO_3$ (25 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **44** (223 mg, 86% yield) as a light yellow foam. *m/z* = 385 (M + 1).

Compound 45: Compound **44** (223 mg, 0.58 mmol) was taken up in ethyl formate (5 mL) and THF (2 mL) and cooled in an ice bath. NaOMe (30 wt. % in MeOH, 1.04 g, 5.8 mmol) was added dropwise, and the solution was allowed to warm to room temperature and stirred overnight. The mixture was cooled in an ice bath, quenched by the addition of saturated aq. KH_2PO_4 (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **45** (265 mg, quantitative yield) as a light yellow foam. *m/z* = 413 (M + 1).

Compound 46: Compound **45** (265 mg, 0.58 mmol) was taken up in EtOH (6 mL). Hydroxylamine hydrochloride (81 mg, 1.16 mmol) was added and the mixture was heated at 50 °C for 3 h, then allowed to cool to room temperature and stirred overnight. The solution was concentrated. Saturated aq. $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **46** (238 mg, quantitative yield) as a yellow foam. *m/z* = 410 (M + 1).

Compound 47: Compound **46** (238 mg, 0.58 mmol) was taken up in THF (10 mL) and MeOH (2 mL) and NaOMe (30 wt. % in MeOH, 1.04 g, 5.8 mmol) was added. The solution was stirred overnight at room temperature and then concentrated. Saturated aq. KH_2PO_4 (25 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated to give 240 mg of a yellow foam. Flash chromatography (silica gel, 2% MeOH/$CHCl_3$) gave compound **47** (181 mg, 76% yield from 44) as a light yellow foam. *m/z* = 410 (M + 1).

Compound T7: Compound **47** (176 mg, 0.43 mmol) was taken up in DMF (4 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (74 mg, 0.26 mmol) was added and the solution was stirred 1 h at 0 °C. Pyridine (0.4 mL) was added and the solution was heated at 60 °C for 3 h. After cooling, saturated aq. $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL).

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The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 160 mg of a brown oil. Flash chromatography (silica gel, 1:1 EtOAc/CH_2Cl_2) gave compound **T7** (85 mg, 54% yield) as a light yellow foam. *m/z* = 408 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.69 (d, 1H, *J* = 7.9 Hz), 7.59 (m, 3H), 7.48 (t, 2H, *J* = 7.5 Hz), 7.41 (m, 2H), 7.18 (d, 1H, *J* = 7.9 Hz), 2.56 (qd, 1H, *J* = 6.6, 13.1 Hz), 2.50 (m, 1H), 2.46 (ddd, 1H, *J* = 6.3, 10.1, 16.4 Hz), 2.32 (s, 3H), 2.12 (dt, 1H, *J* = 2.1, 13.0 Hz), 2.03 (m, 1H), 1.76 (dq, 1H, *J* = 6.4, 12.6 Hz), 1.46 (s, 3H), 1.28 (d, 3H, *J* = 6.7 Hz);

Compound 48: Compound **8** (1 g, 4 mmol) was taken up in benzene (200 mL). 2-Methyl-2*H*-tetrazol-5-amine (475 mg, 4.8 mmol) and $TsOH \cdot H_2O$ (100 mg, 0.5 mmol) were added. The reaction was stirred at refluxing for 2 days. The reaction mixture was filtered, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to give compound **48** (1.05 g, 63% yield) as a foam. *m/z* = 334 (M+1).

Compound 49: Compound **48** (940 mg, 2.8 mmol) was dissolved in EtOH (40 mL). Benzaldehyde (600 mg, 5.6 mmol) and ammonium acetate (2.2 g, 28 mmol) were added. The reaction mixture was stirred for 16 h at room temperature, and then heated at 50 °C for another day. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to give compound **49** (1.05 g, 90% yield) as an off-white solid. *m/z* = 421 (M+1).

Compound 50: Compound **49** (1.05 g, 1.93 mmol) was taken up in THF (5 mL), and 3N HCl (aq, 5 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **50** (940 mg, quantitative yield) as a foam. *m/z* = 377 (M+1).

Compound 51: Compound **50** (940 mg, 2.5 mmol) was taken up in ethyl formate (15 mL, 187.5 mmol). NaOMe (30 wt. % in methanol, 1.7 g, 9.4 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 compound **51** (1 g, quantitative yield) as an oil. *m/z* = 405 (M+1).

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Compound 52: Compound **51** (1 g, 2.5 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (500 mg, 7.2 mmol) was added. The reaction mixture was stirred overnight at 50 ºC. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, then dried with $MgSO_4$, and concentrated to give compound **52** (1 g, quantitative yield) as an oil. *m/z* = 402 (M+1).

Compound 53: Compound **52** (1 g, 2.5 mmol) was dissolved in THF (5 mL), and NaOMe (30 wt. % in methanol, 1.8 g, 10 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **53** (790 mg, 79% yield from **49**) as an oil. *m/z* = 402 (M+1).

Compound T8: Compound **53** (790 mg, 1.96 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. Br_2 (350 mg in 1 mL of dichloromethane, 1.1 eq) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 ml, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 hours, and was concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 40% EtOAc in hexanes) to give compound **T8** (255 mg, 33% yield) as a foam. *m/z* = 400 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.36 (m, 5H), 4.36 (s, 3H), 2.63 (m, 3H), 2.17 (dt, 1H, *J* = 1.8, 12.7 Hz), 2.11 (m, 1H), 1.85 (m, 1H), 1.51 (s, 3H), 1.31 (d, 3H, *J* = 6.7 Hz).

Compound 54: Compound **9** (0.26 g, 0.79 mmol) was taken up in EtOH (6 mL). A solution of 1-methyl-1*H*-pyrazole-4-carbaldehyde (175 mg, 1.59 mmol) in EtOH (1 mL) was added followed by ammonium acetate (612 mg, 7.9 mmol). The mixture was stirred 4 d at room temperature and then concentrated. Saturated $NaHCO_3$ (25 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to give 0.43 g of a dark yellow foam. Flash chromatography (silica gel, 2-5% MeOH/CH_2Cl_2) gave compound **54** (0.29 g, 87% yield) as a white solid. *m/z* = 419 (M + 1).

Compound 55: Compound **54** (290 mg, 0.69 mmol) was taken up in THF (7 mL) and 1M HCl (1 mL) was added. The solution was stirred overnight and then concentrated. Saturated $NaHCO_3$ (20 mL) was added and the mixture was extracted

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with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **55** (250 mg, 97% yield) as a white solid. *m/z* = 375 (M + 1).

Compound 56: Compound **55** (227 mg, 0.61 mmol) was taken up in ethyl formate (5 mL) and cooled in an ice bath. NaOMe (1.09 g, 30 wt. % in MeOH) was added dropwise, and the solution was allowed to warm to room temperature and stirred 4 h. The mixture was cooled in an ice bath, quenched by the addition of saturated aq. KH_2PO_4 (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **56** (265 mg, quantitative yield) as a light tan foam. *m/z* = 403 (M + 1).

Compound 57: Compound **56** (0.61 mmol) was taken up in EtOH (6 mL). Hydroxylamine hydrochloride (85 mg, 1.22 mmol) was added. The mixture was heated at 50 °C for 3 h, then allowed to cool to room temperature and stirred overnight. The solution was concentrated. Saturated aq. $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **57** (250 mg, quantitative yield) as a light yellow foam. *m/z* = 400 (M + 1).

Compound 58: Compound **57** (0.61 mmol) was taken up in THF (10 mL) and MeOH (1 mL) and NaOMe (30 wt. % in MeOH, 1.09 g, 6.1 mmol) was added. The solution was stirred 4 h at room temperature, becoming a thick heterogeneous mixture. Most of the solvent was removed via rotary evaporation. Saturated aq. KH_2PO_4 (25 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated to give 260 mg of a yellow foam. Flash chromatography (silica gel, 4% MeOH/$CHCl_3$) gave compound **58** (232 mg, 95% yield) as a light yellow foam. *m/z* = 400 (M + 1).

Compound T9: Compound **58** (232 mg, 0.58 mmol) was taken up in DMF (5 mL) and cooled in an ice bath. *N,N'*-dibromodimethylhydantoin (83 mg, 0.29 mmol) was added and the solution was stirred 1 h at 0 °C. Pyridine (0.5 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, saturated aq. $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The

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combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 176 mg of an orange solid. Flash chromatography (silica gel, 3% MeOH/$CHCl_3$) gave compound **T9** (101 mg, 44% yield) as a light orange solid. *m/z* = 398 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.51 (m, 3H), 7.34 (s, 1H), 7.25 (m, 2H), 7.06 (s, 1H), 3.81 (s, 3H), 2.57 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.43 (m, 2H), 2.13 (dt, 1H, *J* = 2.3, 12.8 Hz), 2.05 (m, 1H), 1.79 (m, 1H), 1.49 (s, 3H), 1.29 (d, 3H, *J* = 6.8 Hz);

Compound 59: Compound **8** (0.7 g, 2.7 mmol) was taken up in benzene (100 mL). 2-Methyl-aniline (360 mg, 3.4 mmol) and TsOH·H_2O (50 mg, 0.25 mmol) were added. The reaction was stirred at refluxing for 2 days. The reaction mixture was filtered, concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 35% EtOAc in hexanes) to give compound **59** (0.49 g, 53% yield) as an oil. *m/z* = 342 (M+1).

Compound 60: Compound **59** (490 mg, 1.43 mmol) was dissolved in EtOH (10 mL). Acetaldehyde (130 mg, 2.9 mmol) and ammonium acetate (1.1 g, 14 mmol) were added. The reaction mixture was stirred for 16 h at room temperature. Acetaldehyde (130 mg) was added and stirred for 2 days. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 5% MeOH in EtOAc) to give compound **60** (140 mg, 27% yield) as a foam. *m/z* = 367 (M+1).

Compound 61: Compound **60** (140 mg, 0.38 mmol) was taken up in THF (2 mL), and 3N HCl (aq, 2 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give **61** (120 mg, quantitative yield) as a foam. *m/z* = 323 (M+1).

Compound 62: Compound **61** (120 mg, 0.37 mmol) was taken up in ethyl formate (10 mL, 125 mmol). NaOMe (30 wt. % in methanol, 0.3 g, 1.67 mmol) was added. The mixture was stirred overnight at room temperature. The reaction mixture was neutralized with aq. KH_2PO_4, and was extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **62** (130 mg, quantitative yield) as an oil. *m/z* = 351 (M+1).

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Compound 63: Compound **62** (130 mg, 0.37 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (55 mg, 0.8 mmol) was added. The reaction mixture was stirred overnight at 50 ºC. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **63** (130 mg, quantitative yield) as an oil. *m/z* = 348 (M+1).

Compound 64: Compound **63** (130 mg, 0.37 mmol) was dissolved in THF (2 mL), and NaOMe (30 wt. % in methanol, 300 mg, 1.67 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed with brine, then dried with $MgSO_4$, and concentrated to give compound **64** (110 mg, 86% yield from **60**) as an oil. *m/z* = 348 (M+1).

Compound T10: Compound **64** (110 mg, 0.32 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Br_2 (56 mg in 1 mL of dichloromethane, 1.1 eq) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 hours, then concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 5% MeOH in EtOAc) to give compound **T10** (30 mg, 27% yield) as a foam. *m/z* = 346 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 atropisomers) δ [8.57 (s), 8.56 (s)] (1H), 7.35 (m, 4H), [7.15 (d, *J* = 7.4 Hz), 7.09 (d, *J* = 7.4 Hz)] (1H), 2.55 (qd, 1H, *J* = 6.8, 13.4 Hz), 2.18 (m, 3H), 2.14 (s, 3H), [2.01 (s), 1.99 (s)] (3H), 1.75 (m, 1H), [1.45 (s), 1.45 (s)] (3H), 1.28 (d, 3H, *J* = 6.9 Hz).

Compound 65: Compound **9** (0.76 g, 2.32 mmol) was taken up in EtOH (15 mL) and ammonium acetate (1.79 g, 23.2 mmol) was added followed by a solution of 3-(benzyloxy)propanal (762 mg, 4.64 mmol) in EtOH (2 mL). The mixture was stirred overnight at room temperature. An additional portion of 3-(benzyloxy)propanal (240 mg) was added and the mixture was stirred 3 d at room temperature. The mixture was heated at 80 °C for 24 h, then cooled and concentrated. Saturated $NaHCO_3$ (50 mL) was added and the mixture was extracted with EtOAc (2 × 75 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 1.40 g of an orange oil.

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Flash chromatography (silica gel, 2% MeOH/$CHCl_3$) gave compound **65** (384 mg, 35% yield) as a yellow foam. *m/z* = 473 (M + 1).

Compound 66: Compound **65** (384 mg, 0.81 mmol) was taken up in THF (7 mL) and 1M HCl (1 mL) was added. The solution was stirred 3 d and then concentrated. Saturated $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **66** (316 mg, 91% yield) as a yellow oil. *m/z* = 429 (M + 1).

Compound 67: Compound **66** (316 mg, 0.74 mmol) was taken up in ethyl formate (5 mL) and cooled in an ice bath. NaOMe (1.3 g, 30 wt. % in MeOH) was added dropwise, and the solution was allowed to warm to room temperature and stirred 5 h. The mixture was cooled in an ice bath, quenched by the addition of saturated aq. KH_2PO_4 (25 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **67** (336 mg, 99% yield) as a light brown foam. *m/z* = 457 (M + 1).

Compound 68: Compound **67** (336 mg, 0.74 mmol) was taken up in EtOH (6 mL). Hydroxylamine hydrochloride (102 mg, 1.47 mmol) was added and the mixture was heated at 50 °C for 3 h, then cooled and concentrated. Saturated aq. $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **68** (317 mg, 95% yield) as a yellow-brown foam. *m/z* = 454 (M + 1).

Compound 69: Compound **68** (317 mg, 0.70 mmol) was taken up in THF (10 mL) and MeOH (1 mL) and NaOMe (1.26 g, 30 wt. % in MeOH) was added. The solution was stirred 5 h at room temperature and then concentrated. Saturated aq. KH_2PO_4 (25 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated to give 320 mg of a dark yellow foam. Flash chromatography (silica gel, 2% MeOH/$CHCl_3$) gave compound **69** (240 mg, 76% yield) as a yellow foam. *m/z* = 454 (M + 1).

Compound T11: Compound **69** (62 mg, 0.14 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-dibromodimethylhydantoin (20 mg, 0.068 mmol)

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was added and the solution was stirred 1 h at 0 °C. Pyridine (0.1 mL) was added and the solution was heated at 60 ºC for 4 h. After cooling, saturated aq. $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 67 mg of a yellow oil. Flash chromatography (silica gel, 1:3 EtOAc/CH_2Cl_2) gave compound **T11** (32 mg, 52% yield) as a light yellow foam. *m/z* = 452 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.45 (m, 3H), 7.28 (m, 3H), 7.20 (m, 4H), 4.45 (s, 3H), 3.74 (m, 2H), 2.88 (m, 1H), 2.55 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.38 (m, 2H), 2.10 (dt, 1H, *J* = 2.2, 12.8 Hz), 2.02 (m, 1H), 1.75 (m, 1H), 1.45 (s, 3H), 1.28 (d, 3H, *J* = 6.7 Hz).

Compound 70: Compound **69** (165 mg, 0.36 mmol) was taken up in MeOH (10 mL) and placed under nitrogen. 10% Pd/C (40 mg) was added, and the flask was evacuated and purged with hydrogen (3×), then stirred overnight under a hydrogen balloon. 20% $Pd(OH)_2$/C (40 mg) was added, and the mixture was resubjected to hydrogenation for 24 h. Another portion of 20% $Pd(OH)_2$/C (40 mg) was added and the mixture was resubjected to hydrogenation for 48 h. The mixture was filtered through a fine frit and the filtrate was concentrated. Flash chromatography (silica gel, 5% MeOH/$CHCl_3$) gave 55 mg of impure compound **70** as a white foam. This material was re-chromatographed (silica gel, 5% MeOH/EtOAc) to give compound **70** (15 mg, 9% yield) as a white solid. *m/z* = 364 (M + 1).

Compound T12: Compound **70** (15 mg, 0.041 mmol) was taken up in DMF (1 mL) and cooled in an ice bath. *N*,*N*′-dibromodimethylhydantoin (5.9 mg, 0.021 mmol) was added and the solution was stirred 1 h at 0 °C. Pyridine (0.1 mL) was added and the solution was heated at 60 ºC for 4 h. The solution was cooled and concentrated to a brown oil. Flash chromatography (silica gel, 3-5% MeOH/$CHCl_3$) gave compound **T12** (8.6 mg, 58% yield) as a yellow solid. *m/z* = 362 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.50 (m, 3H), 7.20 (m, 2H), 3.93 (m, 2H), 2.71 (m, 2H), 2.56 (qd, 1H, *J* = 6.8, 13.4 Hz), 2.41 (m, 2H), 2.11 (dt, 1H, *J* = 2.3, 12.9 Hz), 2.02 (m, 1H), 1.76 (m, 1H), 1.58 (br s, 1H), 1.44 (s, 3H), 1.28 (d, 3H, *J* = 6.8 Hz).

Compound 71: Compound **8** (0.5 g, 2 mmol) was taken up in benzene (100 mL). 1-Methyl-1*H*-pyrazol-4-amine (250 mg, 2.57 mmol) and $TsOH \cdot H_2O$ (50 mg, 0.25 mmol) were added. The reaction was stirred at refluxing for 2 days, and was

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filtered, concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 35% EtOAc in hexanes) to give compound **71** (0.52 g, 79% yield) as an oil. *m/z* = 332 (M+1).

Compound 72: Compound **71** (520 mg, 1.56 mmol) was dissolved in EtOH (10 mL). Acetaldehyde (150 mg, 3.4 mmol) and ammonium acetate (1.3 g, 17 mmol) were added. The reaction mixture was stirred for 16 h at room temperature. Acetaldehyde (150 mg) was added and stirring continued for 2 days. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 5% MeOH in EtOAc) to give compound **72** (520 mg, 93% yield) as a solid. *m/z* = 357 (M+1).

Compound 73: Compound **72** (520 mg, 1.46 mmol) was taken up in THF (5 mL), and 3N HCl (aq, 3 mL) was added. The mixture was stirred overnight at room temperature, then concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and was extracted with ethyl acetate. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **73** (455 mg, quantitative yield) as a foam. *m/z* = 313 (M+1).

Compound 74: Compound **73** (455 mg, 1.46 mmol) was taken up in ethyl formate (15 mL, 187.5 mmol). NaOMe (30 wt. % in methanol, 1.05 g, 6 mmol) was added. The mixture was stirred overnight at room temperature, neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **74** (495 mg, quantitative yield) as an oil. *m/z* = 341 (M+1).

Compound 75: Compound **74** (495 mg, 1.46 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (205 mg, 3 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **75** (485 mg, quantitative yield) as an oil. *m/z* = 338 (M+1).

Compound 76: Compound **75** (485 mg, 1.46 mmol) was dissolved in THF (2 mL), and NaOMe (30 wt. % in methanol, 1.05 g, 5.8 mmol) was added. The reaction mixture was stirred at room temperature overnight. The reaction was neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract

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was washed with brine, dried with $MgSO_4$, and concentrated to give compound **76** (380 mg, 77% yield from **72**) as a solid. *m/z* = 338 (M+1).

Compound T13: Compound **76** (380 mg, 1.12 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Br_2 (200 mg in 1 mL of dichloromethane, 1.1 eq) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 h, then concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 5% MeOH in EtOAc) to give compound **T13** (135 mg, 36% yield) as a foam. *m/z* = 336 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.48 (s, 1H), 7.44 (s, 1H), 3.98 (s, 3H), 2.54 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.42 (m, 2H), 2.29 (s, 3H), 2.06 (m, 2H), 1.74 (m, 1H), 1.43 (s, 3H), 1.28 (d, 3H, *J* = 6.7 Hz).

Compound 77: Compound **8** (1.8 g, 7.1 mmol) was taken up in benzene (200 mL). (*E*)-Methyl 3-(3-aminophenyl) acrylate (1.6 g, 9 mmol) and $TsOH{\cdot}H_2O$ (150 mg, 0.75 mmol) were added. The reaction was stirred at refluxing for 16 h. The reaction mixture was filtered, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to give compound **77** (2.7 g, 92% yield) as an oil. *m/z* = 412 (M+1).

Compound 78: Compound **77** (2.6 g, 6.3 mmol) was dissolved in EtOH (100 mL). Acetaldehyde (560 mg, 12.6 mmol) and ammonium acetate (4.8 g, 63 mmol) were added. The reaction mixture was stirred for 16 h at room temperature. Acetaldehyde (560 mg) was added and stirred for another day. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 5% MeOH in EtOAc) to give compound **78** (800 mg, 29% yield) as an oil. *m/z* = 437 (M+1).

Compound 79: Compound **78** (800 mg, 1.83 mmol) was taken up in THF (10 mL), and 3N HCl (aq, 5 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated, neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **79** (650 mg, 90% yield) as a foam. *m/z* = 393 (M+1).

Compound 80: Compound **79** (650 mg, 1.65 mmol) was taken up in ethyl formate (15 mL, 187.5 mmol). NaOMe (30 wt. % in methanol, 0.8 g, 4.4 mmol) was

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added. The mixture was stirred overnight at room temperature, neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **80** (685 mg, 95% yield) as a foam. *m/z* = 435 (M+1).

Compound 81: Compound **80** (685 mg, 1.57 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (250 mg, 3.6 mmol) was added. The reaction mixture was stirred overnight at 50 °C, cooled to room temperature, and concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **81** (642 mg, 95% yield) as an oil. *m/z* = 432 (M+1).

Compound 82 and 83: Compound **81** (642 mg, 1.48 mmol) was dissolved in THF (10 mL), and NaOMe (30 wt. % in methanol, 1.1 g, 6 mmol) was added. The reaction mixture was stirred at room temperature overnight, then neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated to give a mixture of compound **82** and compound **83** (485 mg) as an oil. *m/z* = 418 (M+1 for **82)** and 404 (M+1 for **83**).

Compound 84 and 85: The mixture of compound **82** and **83** (480 mg) was hydrogenated at atmospheric pressure in EtOAc/THF (10:1, 22 mL) over 10% Pd/C (35 mg) for 16 h at room temperature. The reaction mixture was filtered using a Celite pad. The filtrate was concentrated, purified by column chromatography (silica gel, 0 to 15% MeOH in EtOAc) to isolate compound **84** (184 mg, 29% yield from **81**) and compound **85** (169 mg, 28% yield from **81**) as an oil. Compound **84**: *m/z* = 420 (M+1); Compound **85**: *m/z* = 406 (M+1).

Compound T14: Compound **84** (184 mg, 0.458 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. Br_2 (80 mg in 1 mL of dichloromethane, 1.1 eq) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 50 to 100% EtOAc in hexanes) to give compound **T14** (50 mg, 27% yield) as a foam. *m/z* = 418 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.42 (m, 1H), 7.30 (d, 1H, *J* = 8.0 Hz), 7.05 (m, 2H), 3.67 (s, 3H), 3.02 (t, 2H, *J* = 7.6 Hz), 2.67 (t, 2H, *J* = 7.6 Hz), 2.55 (qd, 1H, *J* = 6.7, 13.4 Hz), 2.39 (m, 2H), 2.26 (s, 3H),

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2.10 (dt, 1H, J = 2.2, 12.9 Hz), 2.02 (m, 1H), 1.74 (m, 1H), 1.45 (s, 3H), 1.28 (d, 3H, J = 6.8 Hz).

Compound T15: Compound **85** (160 mg, 0.39 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. Br_2 (70 mg in 1 mL of dichloromethane, 1.1 eq) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 hours. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 15% MeOH in EtOAc) to give compound **T15** (25 mg, 16% yield) as a foam. m/z = 404 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.44 (t, 1H, J = 7.7 Hz), 7.35 (d, 1H, J = 7.7 Hz), 7.15 (s, 1H), 7.02 (d, 1H, J = 8.0 Hz), 3.06 (t, 2H, J = 6.6 Hz), 2.72 (t, 2H, J = 6.6 Hz), 2.53 (qd, 1H, J = 6.7, 13.4 Hz), 2.39 (m, 2H), 2.15 (s, 3H), 2.05 (m, 2H), 1.71 (m, 1H), 1.40 (s, 3H), 1.27 (d, 3H, J = 6.9 Hz).

Compound 86: Compound **48** (228 mg, 0.68 mmol) was taken up in THF (2 mL) and EtOH (2 mL). Ammonium acetate (524 mg, 6.8 mmol) was added followed by a solution of 1-methyl-1*H*-pyrazole-4-carbaldehyde (150 mg, 1.36 mmol) in EtOH (1 mL). The mixture was stirred 7 d at room temperature. Saturated $NaHCO_3$ (25 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to give 0.47 g of a yellow oil. Flash chromatography (silica gel, 2-5% MeOH/CH_2Cl_2) gave impure compound **86** (85 mg, 29% yield) as a yellow oil. m/z = 425 (M + 1).

Compound 87: Impure compound **86** (85 mg, 0.20 mmol) was taken up in THF (3 mL) and 1M HCl (0.5 mL) was added. The solution was stirred 3 d at room temperature, saturated $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 80 mg of an oil. Flash chromatography (silica gel, 2-5% MeOH/$CHCl_3$) gave compound **87** (45 mg, 59% yield) as a white foam. m/z = 381 (M + 1).

Compound 88: Compound **87** (45 mg, 0.12 mmol) was taken up in ethyl formate (2 mL) and cooled in an ice bath. NaOMe (0.21 g, 30 wt. % in MeOH) was added dropwise, and the solution was allowed to warm to room temperature and stirred 2 h. The mixture was cooled in an ice bath, quenched by the addition of saturated aq. KH_2PO_4 (20 mL), and extracted with EtOAc (2 × 50 mL). The

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combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give compound **88** (48 mg, quantitative yield) as a light yellow foam. *m/z* = 409 (M + 1).

Compound 89: Compound **88** (48 mg, 0.12 mmol) was taken up in EtOH (2 mL). Hydroxylamine hydrochloride (25 mg, 0.36 mmol) was added and the mixture was heated at 50 °C for 4 h, then allowed to cool to room temperature and stirred overnight. The solution was concentrated, saturated aq. $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO4, concentrated, and dried under vacuum to give compound **89** (44 mg, 92% yield from **87**) as a light yellow foam. *m/z* = 406 (M + 1).

Compound 90: Compound **89** (44 mg, 0.11 mmol) was taken up in THF (3 mL) and MeOH (1 mL) and NaOMe (0.21 g, 30 wt. % in MeOH) was added. The solution was stirred 6 h at room temperature, and most of the solvent was removed via rotary evaporation. Saturated aq. KH_2PO_4 (20 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated to give 44 mg of a light yellow foam. Flash chromatography (silica gel, $CHCl_3$ then 2% MeOH/$CHCl_3$) gave compound **90** (33 mg, 75% yield) as a pale yellow glass. *m/z* = 406 (M + 1).

Compound T16: Compound **90** (33 mg, 0.081 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N*,*N*'-dibromodimethylhydantoin (11.6 mg, 0.041 mmol) was added and the solution was stirred 1 h at 0 °C. Pyridine (0.1 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, saturated aq. $NaHCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, concentrated, and dried under vacuum to give 27 mg of a brown oil. Flash chromatography (silica gel, 2% MeOH/$CHCl_3$) gave compound **T16** (12 mg, 37% yield) as a light yellow foam. *m/z* = 404 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.72 (s, 1H), 7.43 (s, 1H), 4.42 (s, 3H), 3.90 (s, 3H), 2.60 (m, 3H), 2.12 (m, 2H), 1.84 (m, 1H), 1.48 (s, 3H), 1.31 (d, 3H, *J* = 6.7 Hz).

Compound 91: Compound **71** (380 mg, 1.14 mmol) was dissolved in EtOH (10 mL). Benzaldehyde (250 mg, 2.3 mmol) and ammonium acetate (0.9 g, 11 mmol) were added. The reaction mixture was stirred for 16 h at room temperature, then

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concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 25 to 100% EtOAc in hexanes) to give compound **91** (420 mg, 88% yield) as a solid. *m/z* = 419 (M+1).

Compound 92: Compound **91** (420 mg, 1 mmol) was taken up in THF (5 mL), and 3N HCl (aq, 3 mL) was added. The mixture was stirred overnight at room temperature, then concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **92** (385 mg, quantitative yield) as a solid. *m/z* = 375 (M+1).

Compound 93: Compound **92** (385 mg, 1 mmol) was taken up in ethyl formate (15 mL, 187.5 mmol). NaOMe (30 wt. % in methanol, 0.75 g, 4 mmol) was added. The mixture was stirred overnight at room temperature, neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **93** (410 mg, quantitative yield) as a solid. *m/z* = 403 (M+1).

Compound 94: Compound **93** (410 mg, 1 mmol) was dissolved in EtOH. Hydroxylamine hydrochloride (140 mg, 2 mmol) was added. The reaction mixture was stirred overnight at 50 ºC, cooled to room temperature, and concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **94** (400 mg, quantitative yield) as an oil. *m/z* = 400 (M+1).

Compound 95: Compound **94** (400 mg, 1 mmol) was dissolved in THF (5 mL), and NaOMe (30 wt. % in methanol, 0.75 g, 4 mmol) was added. The reaction mixture was stirred at room temperature overnight, neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated to give compound **95** (400 mg, quantitative yield) as a solid. *m/z* = 400 (M+1).

Compound T17: Compound **95** (400 mg, 1 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. Br_2 (180 mg in 1 mL of dichloromethane, 1.1 eq) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 hours, then concentrated. The crude residue was purified by column chromatography (silica gel,

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50 to 100% EtOAc in hexanes) to give compound **T17** (185 mg, 46% yield from **91**) as a foam. *m/z* = 398 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.46 (m, 3H), 7.30 (m, 4H), 3.91 (s, 3H), 2.58 (qd, 1H, *J* = 6.85, 13.5 Hz), 2.51(m, 2H), 2.13 (dt, 1H, *J* = 2.2, 12.9 Hz), 2.09 (m, 1H), 1.82 (m, 1H), 1.50 (s, 3H), 1.31 (d, 3H, *J* = 6.8 Hz).

Compound T18: Compound **T15** (75 mg, 0.18 mmol) was dissolved in dichloromethane (5 mL) at 0 °C. Oxalyl chloride (120 mg, 0.94 mmol) and DMF (1 drop) were added, and the solution was stirred for 1 h. After evaporation of the solvent, the crude carbonyl chloride was obtained. The crude carbonyl chloride in dichloromethane (2 mL) was added to a solution of $MeNH_2$ (30 wt. % in water, 0.3 g, 2.8 mmol) in THF (5 mL) at 0 ºC, then stirred at room temperature for 16 h. The reaction mixture was concentrated, diluted with saturated $NaHCO_3$ and extracted with EtOAc (2 × 65 mL). Combined organic extracts were dried with $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 0 to 10% MeOH in EtOAc) to give compound **T18** (25 mg, 32% yield) as a foam. *m/z* = 417 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.41 (t, 1H, *J* = 7.7 Hz), 7.30 (m, 1H), 7.04 (m, 2H), 5.34 (br s, 1H), 3.04 (t, 2H, *J* = 7.5 Hz), 2.79 (d, 3H, *J* = 4.9 Hz), 2.49 (t, 2H, *J* = 7.5 Hz), 2.47 (m, 3H), 2.25 (s, 3H), 2.10 (dt, 1H, *J* = 2.3, 12.3 Hz), 2.02 (m, 1H), 1.75 (m, 1H), 1.44 (s, 3H), 1.28 (d, 3H, *J* = 6.9 Hz).

Compound T19: Compound **T15** (100 mg, 0.24 mmol) was dissolved in dichloromethane (5 mL) at 0 ºC. Oxalyl chloride (150 mg, 1.18 mmol) and DMF (1 drop) were added, and the solution was stirred for 1 h. After evaporation of the solvent, the crude carbonyl chloride was obtained. The crude carbonyl chloride in dichloromethane (2 mL) was added to a solution of Me_2NH (2M, 1 mL, 2 mmol) in dichloromethane (5 mL) at 0 ºC, then stirred at room temperature for 16 h. The reaction mixture was concentrated, diluted with saturated $NaHCO_3$, and extracted with EtOAc (2 × 65 mL). Combined organic extracts were dried with $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 0 to 10% MeOH in EtOAc) to give compound **T19** (40 mg, 38% yield) as a foam. *m/z* = 431 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.40 (t, 1H, *J* = 7.7 Hz), 7.31 (d, 1H, *J* = 7.8 Hz), 7.05 (m, 2H), 3.04 (t, 2H, *J* = 7.6 Hz), 2.97 (s, 3H), 2.95 (s, 3H), 2.64 (t, 2H, *J* = 7.6 Hz), 2.54 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.40 (m, 2H), 2.25 (s, 3H), 2.09 (dt, 1H, *J* = 2.3, 13.0 Hz), 2.01 (m, 1H), 1.74 (ddd, 1H, *J* = 6.7, 12.9, 18.0 Hz), 1.44 (s, 3H), 1.27 (d, 3H, *J* = 6.7 Hz).

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Compound T20: Compound **T15** (75 mg, 0.18 mmol) was dissolved in dichloromethane (5 mL) at 0 ºC. Oxalyl chloride (120 mg, 5 eq) and DMF (1 drop) were added, and the solution was stirred for 1 h. After evaporation of the solvent, the crude carbonyl chloride was obtained. The crude carbonyl chloride in dichloromethane (2 mL) was added to a solution of NH_4OH (30 wt. %, 0.2 g, 3 mmol) in THF (5 mL) at 0 ºC, then stirred at room temperature for 16 h. The reaction mixture was concentrated, diluted with saturated $NaHCO_3$, and extracted with EtOAc (2 × 65 mL). Combined organic extracts were dried with $MgSO_4$, concentrated, and purified by column chromatography (silica gel, 0 to 10% MeOH in EtOAc) to give compound **T20** (10 mg, 10% yield) as a foam. *m/z* = 403 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.42 (t, 1H, *J* = 7.7 Hz), 7.31 (d, 1H, *J* = 7.9 Hz), 7.06 (m, 2H), 5.29 (br s, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.57 (t, 2H, *J* = 7.6 Hz), 2.43 (m, 3H), 2.26 (s, 3H), 2.06 (m, 2H), 1.74 (m, 1H), 1.44 (s, 3H), 1.28 (d, 3H, *J* = 6.8 Hz).

Compound 96: Compound **8** (1.0 g, 3.96 mmol) was mixed in EtOH (15 mL) along with ammonium acetate (3.0 g, 39 mmol) and acetaldehyde (350 mg, 7.95 mmol), and the mixture was stirred for 16 h. The mixture was concentrated, quenched with saturated $NaHCO_3$, and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (silica gel, 0-10% MeOH/EtOAc) to give compound **96** (0.85 g, 77% yield) as an oil. *m/z* = 277 (M + 1).

Compound 97: Compound **96** (330 mg, 1.2 mmol) was mixed with cesium carbonate (1.5 g, 4.6 mmol) in acetonitrile (35 mL). 1-Bromo-3-methoxypropane (300 mg, 1.96 mmol) was added and the mixture was heated at 85 °C for 16 h. The mixture was cooled and filtered. The filtrate was concentrated and purification by flash chromatography (silica gel, 0-10% MeOH/EtOAc) to give compound **97** (385 mg, 92% yield) as an oil. *m/z* = 349.21 (M + 1).

Compound 98: Compound **97** (385 mg, 1.10 mmol) was taken up in THF (5 mL) and 3N HCl (5 mL) was added. The mixture was stirred for 16 h, then concentrated, diluted with saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 65 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give compound **98** (290 mg, 79% yield) as an oil. *m/z* = 305 (M + 1).

Compound 99: Compound **98** (290 mg, 0.95 mmol) was taken up in ethyl formate (15 mL) and NaOMe (30 wt. % in MeOH, 685 mg, 3.80 mmol) was added dropwise. After stirring at room temperature overnight, the reaction mixture was

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concentrated, quenched with saturated aq. KH_2PO_4, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to give compound **99** (250 mg, 79% yield) as an oil. *m/z* = 333 (M + 1).

Compound 100: Compound **99** (250 mg, 0.75 mmol) was taken up in EtOH (50 mL). Hydroxylamine hydrochloride (110 mg, 1.58 mmol) was added, and the mixture was heated at 50 °C for 16 h. The solution was cooled and concentrated. Saturated $NaHCO_3$ was added, and the mixture was extracted with EtOAc (2 × 65 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give compound **100** (215 mg, 87% yield) as a foam. *m/z* = 330 (M + 1).

Compound 101: Compound **100** (215 mg, 0.65 mmol) was taken up in THF (2 mL) and NaOMe (470 mg, 30 wt. % in MeOH) was added. The solution was stirred at room temperature for 16 h and then concentrated. Saturated aq. KH_2PO_4 was added, and the mixture was extracted with EtOAc (2 × 65 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to give compound **101** (200 mg, 93% yield) as a foam. *m/z* = 330 (M + 1).

Compound T21: Compound **101** (200 mg, 0.61 mmol) was taken up in DMF (4 mL) and cooled in an ice bath. A solution of bromine (110 mg, 0.69 mmol) in dichloromethane (1 mL) was added and the solution was stirred 2 h at 0 °C. Pyridine (2 mL) was added and the solution was heated at 50 °C for 12 h. The solution was cooled and concentrated. Dichloromethane (2 mL) was added followed by saturated aq. $NaHCO_3$ (0.5 mL) and the mixture was stirred for 30 min. The crude product was purified by column chromatography (silica gel, 0 to 2.5 to 5% MeOH/EtOAc) to give compound **T21** (30 mg, 15% yield) as a light orange gum. *m/z* = 328 (M + 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 3.83 (m, 2H), 3.34 (s, 3H), 3.33 (m, 2H), 2.57 (m, 3H), 2.38 (s, 3H), 2.05 (m, 2H), 1.85 (m, 3H), 1.37 (s, 3H), 1.29 (d, 3H, *J* = 6.7 Hz).

Compound 102: To a solution of compound **8** (336 mg, 1.33 mmol) in benzene (16 mL) was added 3-pyrimidin-5-ylaniline (250 mg, 1.47 mmol), followed by *p*-toluenesulfonic acid monohydrate (51 mg, 0.27 mmol). The reaction mixture was stirred at 80 °C for 3 days under N_2. The reaction mixture was concentrated, dissolved in dichloromethane (100 mL) and then washed with saturated $NaHCO_3$ solution (2 × 25 mL). The organic extract was washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated to give a residue. Purification by flash

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chromatography (silica gel, 1 to 1.25% MeOH in dichloromethane) afforded compound **102** (419 mg, 78% yield) as a yellow foamy solid. *m/z* = 406 (M+1).

Compound 103: To a solution of **102** (412 mg, 1.02 mmol) in a mixture of ethanol (3 mL) and tetrahydrofuran (4 mL) was added ammonium acetate (786 mg, 10.20 mmol), followed by acetaldehyde (180 mg, 4.08 mmol). The reaction mixture was stirred in a closed cap vial at room temperature for 5 days. Additional acetaldehyde was added as needed to drive the reaction to completion. The reaction mixture was concentrated, diluted with saturated $NaHCO_3$ solution (50 mL) and then extracted with ethyl acetate (3 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and then concentrated to give a red oil. Purification by flash chromatography (silica gel, 1 to 5% MeOH in dichloromethane) afforded compound **103** (249 mg, 57% yield) as a light yellow tacky solid. *m/z* = 431 (M+1).

Compound 104: To a solution of compound **103** (249 mg, 0.578 mmol) in tetrahydrofuran (5 mL) was added 3 M aq. HCl (1.0 mL, 3.0 mmol). The reaction mixture was stirred at room temperature for 18 h under N_2. The reaction mixture was concentrated, diluted with saturated $NaHCO_3$ solution (25 mL) and then extracted with ethyl acetate (4 × 100 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give compound **104** (222 mg, 99% yield) as a yellow solid, which was used in the next step without further purification. *m/z* = 387 (M+1, 100%).

Compound 105: To a cold (5 °C) solution of compound **104** (222 mg, 0.574 mmol) in a mixture of ethyl formate (5 mL) and tetrahydrofuran (2 mL) was added sodium methoxide (5.4 M solution in MeOH, 1.06 mL, 5.74 mmol). The reaction mixture was stirred for 3 days under N_2 at room temperature, then quenched with saturated KH_2PO_4 (10 mL), diluted with water (25 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give compound **105** (234 mg, 98% yield) as a yellow foamy solid, which was used in the next step without further purification. *m/z* = 415 (M+1).

Compound 106: To a solution of compound **105** (234 mg, 0.565 mmol) in ethanol (6 mL) was added hydroxylamine hydrochloride (78 mg, 1.13 mmol). The reaction mixture was stirred at 50 °C under N_2 for 18 h. The reaction mixture was concentrated, diluted with saturated $NaHCO_3$ solution (25 mL) and then extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with

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brine (50 mL), dried (Na_2SO_4), filtered and then concentrated to give a residue. Purification by flash chromatography (silica gel, 2 to 3% MeOH in dichloromethane) afforded compound **106** (152 mg, 65% yield) as a light yellow solid. *m/z* = 412 (M+1).

Compound 107: To a solution of compound **106** (152 mg, 0.369 mmol) in a mixture of tetrahydrofuran (6 mL) and methanol (1.2 mL) was added sodium methoxide (5.4 M solution in MeOH, 0.68 mL, 3.69 mmol). After stirring at room temperature under N_2 for 18 h, the reaction mixture was concentrated, diluted with saturated KH_2PO_4 solution (20 mL) and then extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to afford compound **107** (152 mg, quantitative yield) as a yellow solid. *m/z* = 412 (M+1).

Compound T22: To a solution of compound **107** (150 mg, 0.36 mmol) in anhydrous N,N-dimethylformamide (4 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (63 mg, 0.22 mmol). The reaction mixture was stirred at 0 °C for 1 h. Pyridine (0.40 mL) was added and then the reaction mixture was stirred at 60 °C for 3 h. The reaction mixture was diluted with saturated $NaHCO_3$ (20 mL) and then extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to afford a residue. Purification by flash chromatography (silica gel, 1 to 2% MeOH in dichloromethane) afforded compound **T22** (79 mg, 54% yield) as an off-white solid. *m/z* = 410 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.98 (s, 2H), 8.55 (s, 1H), 7.69 (m, 2H), 7.44 (s, 1H), 7.34 (m, 1H), 2.49 (m, 3H), 2.33 (s, 3H), 2.10 (m, 2H), 1.77 (m, 1H), 1.46 (s, 3H), 1.29 (d, 3H, *J* = 7.0 Hz).

Compound 108: Compound **9** (3.7 g, 11.3 mmol) was dissolved in EtOH (20 mL). Formaldehyde (37 wt. % in water, 1.5 g, 16.8 mmol) and ammonium acetate (9 g, 116 mmol) were added. The reaction mixture was stirred for 16 h at room temperature. Formaldehyde (1.5 g) was added and stirred for another 2 days. The reaction mixture was concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 10% MeOH in EtOAc) to give compound **108** (3.7 g, 96% yield) as a foam. *m/z* = 339 (M+1).

Compound 109: Compound **108** (430 mg, 1.27 mmol) was dissolved in dry acetonitrile (10 mL), and the solution was cooled to 0 °C. NBS (265 mg, 1.5 mmol)

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was added, and the reaction was stirred at 0 °C for 1 h. The reaction was allowed to warm to room temperature and stirred for 16 h. After concentration, the crude residue was purified by column chromatography (silica gel, 0 to 35% EtOAc in hexane) to give compound **109** (510 mg, 96% yield) as an off-white solid. *m/z* = 417, 419 (1:1, M+1).

Compound 110: Compound **109** (160 mg, 0.38 mmol) was taken up in THF (5 mL), and 3N aq. HCl (3 mL) was added. The mixture was stirred overnight at room temperature, then concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, then dried with $MgSO_4$, and concentrated to give compound **110** (140 mg, quantitative yield) as a foam. *m/z* = 373, 375 (M+1).

Compound 111: Compound **110** (140 mg, 0.38 mmol) was taken up in ethyl formate (10 mL, 125 mmol), and NaOMe (30 wt. % in methanol, 0.25 g, 1.5 mmol) was added. The mixture was stirred overnight at room temperature, then neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **111** (100 mg, 66% yield) as a foam. *m/z* = 401, 403 (M+1).

Compound 112: Compound **111** (100 mg, 0.25 mmol) was dissolved in EtOH (15 mL), and hydroxylamine hydrochloride (35 mg, 0.5 mmol) was added. The reaction mixture was stirred overnight at 50 °C, then cooled to room temperature, and concentrated. The residue was taken up in ethyl acetate, washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **112** (100 mg) as a foam. *m/z* = 398, 400 (M+1).

Compound 113: Compound **112** (100 mg, 0.25 mmol) was dissolved in THF (5 mL), and NaOMe (30 wt.% in methanol, 0.18 g, 1 mmol) was added. The reaction mixture was stirred at room temperature overnight, then neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated to give compound **113** (100 mg) as a foam. *m/z* = 398, 400 (M+1).

Compound T23: Compound **113** (100 mg, 0.25 mmol) was dissolved in dry DMF (2 mL), and the solution was cooled to 0 °C. Bromine (45 mg in 1 mL of dichloromethane, 0.28 mmol) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 h. After concentration,

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the crude residue was purified by column chromatography (silica gel, 5 to 35% EtOAc in hexanes) to give compound **T23** (33 mg, 33% yield from **111**) as a foam. *m/z* = 396, 398 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.52 (m, 3H), 7.25 (m, 2H), 2.55 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.44 (m, 2H), 2.11 (dt, 1H, *J* = 2.3, 12.8 Hz), 2.03 (m, 1H), 1.76 (m, 1H), 1.46 (s, 3H), 1.28 (d, 3H, *J* = 6.8 Hz).

Compound 114: Compound **109** (350 mg, 0.81 mmol) was taken up in dioxane/DMF (4:1, 10 mL). K_2CO_3 (370 mg, 2.53 mmol), $Pd(dppf)Cl_2$ (60 mg, 0.08 mmol) and pyridin-4-ylboronic acid (200 mg, 1.6 mmol) were added. The reaction mixture was bubbled with N_2 for 10 min. After stirring at 100 ºC for 16 h, the reaction mixture was filtered, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 10% MeOH in EtOAc) to give compound **114** (320 mg, 98% yield) as a solid. *m/z* = 416 (M+1).

Compound 115: Compound **114** (320 mg, 0.8 mmol) was taken up in THF (7 mL), and 3N HCl (aq, 3 mL) was added. After stirring overnight at room temperature, the reaction mixture was concentrated. The residue was neutralized with saturated aq. $NaHCO_3$, and extracted with ethyl acetate. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **115** (200 mg, 70% yield) as a foam. *m/z* = 372 (M+1).

Compound 116: Compound **115** (200 mg, 0.54 mmol) was taken up in ethyl formate (15 mL, 187.5 mmol), and NaOMe (30 wt. % in methanol, 0.4 g, 2.2 mmol) was added. The mixture was stirred overnight at room temperature, then neutralized with aq. KH_2PO_4, and extracted with ethyl acetate. The organic extract was dried with $MgSO_4$ and concentrated to give compound **116** (205 mg, 94% yield) as a solid. *m/z* = 400 (M+1).

Compound 117: Compound **116** (205 mg, 0.5 mmol) was dissolved in EtOH (15 mL), and hydroxylamine hydrochloride (70 mg, 1 mmol) was added. The reaction mixture was stirred overnight at 50 ºC. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in ethyl acetate, then washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated to give compound **117** (200 mg) as a foam. *m/z* = 397 (M+1).

Compound 118: Compound **117** (200 mg, 0.5 mmol) was dissolved in THF (5 mL), and NaOMe (30 wt. % in methanol, 0.36 g, 2 mmol) was added. The reaction mixture was stirred at room temperature overnight, then neutralized by addition of saturated KH_2PO_4, and extracted with ethyl acetate. The organic extract was washed

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with brine, dried with $MgSO_4$, and concentrated to give compound **118** (200 mg) as an oil. *m/z* = 397 (M+1).

Compound T24: Compound **118** (200 mg, 0.5 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. Bromine (90 mg in 1 mL of dichloromethane, 0.56 mmol) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (2 mL, 26 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 h. After concentration, the crude residue was purified by column chromatography (silica gel, 0 to 10% MeOH in EtOAc) to give compound **T24** (85 mg, 43% yield from **116**) as an off-white solid. *m/z* = 395 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.46 (m, 2H), 7.51 (m, 3H), 7.22 (m, 4H), 2.59 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.50 (dd, 2H, *J* = 4.0, 8.7 Hz), 2.15 (dt, 1H, *J* = 2.3, 12.7 Hz), 2.09 (m, 1H), 1.82 (tt, 1H, *J* = 8.9, 13.4 Hz), 1.55 (s, 3H), 1.30 (d, 3H, *J* = 6.8 Hz).

Compound 119: To a solution of compound **48** (350 mg, 1.05 mmol) in a mixture of tetrahydrofuran (3 mL) and ethanol (4 mL) was added ammonium acetate (809 mg, 10.50 mmol), followed by *o*-tolualdehyde (1.010 g, 8.40 mmol). The reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated, diluted with saturated aq. $NaHCO_3$ solution (25 mL) and then extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give a red oil. Purification by flash chromatography (silica gel, 2 to 17% EtOAc in dichloromethane) afforded compound **119** (377 mg, 83% yield) as a yellow tacky solid. *m/z* = 435 (M+1).

Compound 120: To a solution of compound **119** (255 mg, 0.587 mmol) in tetrahydrofuran (5 mL) was added 3M aq. HCl (1.0 mL, 3 mmol). The reaction mixture was stirred at room temperature for 3.5 h under N_2, then diluted with saturated aq. $NaHCO_3$ solution (25 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give compound **120** (250 mg, quantitative) as a yellow-green tacky solid, which was used in the next step without further purification. *m/z* = 391 (M+1).

Compound 121: To a 0 °C solution of compound **120** (250 mg, 0.640 mmol) in a mixture of ethyl formate (5 mL) and tetrahydrofuran (2 mL) was added sodium methoxide (5.4 M solution in methanol, 1.19 mL, 6.40 mmol). The reaction mixture

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was stirred for 18 h under N_2 at room temperature, then quenched with saturated KH_2PO_4 (25 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give compound **121** (252 mg, 94% yield) as a yellow-orange foamy solid, which was used in the next step without further purification. *m/z* = 419 (M+1).

Compound 122: To a solution of compound **121** (252 mg, 0.602 mmol) in ethanol (6 mL) was added hydroxylamine hydrochloride (84 mg, 1.20 mmol). The reaction mixture was stirred at 50 °C under N_2 for 18 h, then concentrated, diluted with saturated aq. $NaHCO_3$ solution (25 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to give a residue. Purification by flash chromatography (silica gel, 9 to 50% EtOAc in hexanes) afforded compound **122** (105 mg, 42% yield) as an off-white tacky solid. *m/z* = 416 (M+1).

Compound 123: To a solution of compound **122** (103 mg, 0.248 mmol) in a mixture of tetrahydrofuran (5 mL) and methanol (1 mL) was added sodium methoxide (5.4 M solution in methanol, 0.46 mL, 2.48 mmol). The reaction mixture was stirred at room temperature under N_2 for 18 h, then concentrated. The residue was diluted with saturated KH_2PO_4 solution (20 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to afford compound **123** (115 mg) as a yellow solid, which was used in the next step without further purification. *m/z* = 416 (M+1).

Compound T25: To a solution of compound **123** (115 mg, 0.28 mmol) in anhydrous N,N-dimethylformamide (4 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (48 mg, 0.17 mmol). The reaction mixture was stirred at 0 °C for 1 h. Pyridine (0.40 mL) was added and then the reaction mixture was stirred at 60 °C for 2.5 h. The reaction mixture was diluted with saturated aq. $NaHCO_3$ (20 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated to afford a residue. Purification by flash chromatography (silica gel, 1 to 25% MeOH in dichloromethane) afforded compound **T25** (48 mg, 42% yield from **122**) as a yellow solid. *m/z* = 414 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.46 (m, 2H), 7.51 (m, 3H), 7.22 (m, 4H), 2.59 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.50 (dd, 2H, *J* = 4.0, 8.7 Hz), 2.15 (dt, 1H, *J* = 2.3, 12.7 Hz), 2.09 (m, 1H), 1.82 (tt, 1H, *J* = 8.9, 13.4 Hz), 1.55 (s, 3H), 1.30 (d, 3H, *J* = 6.8 Hz).

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Compound 124: A mixture of compound **109** (0.50 g, 1.26 mmol), zinc cyanide (0.15 g, 1.28 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.060 g, 0.066 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (0.040 g, 0.072 mmol) in DMF (3 mL) was degassed then microwaved at 180 °C for 5 min. The sample was cooled, diluted with ethyl acetate (3 mL), filtered, concentrated and chromatographed (silica gel, 0 to 35% EtOAc in hexanes) to give compound **124** (0.380 g, 88% yield) as an off-white solid. *m/z* = 364 (M+1).

Compound 125: A solution of compound **124** (0.55 g, 1.51 mmol) and 1N aq. HCl (15 mL, 15 mmol) in methanol:THF (1:1, 30 mL) was stirred at room temperature under N_2 overnight. The sample was concentrated, cooled, basified with 10% NH_4OH solution to pH ~ 9-10, then extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give compound **125** (0.66 g) as yellow oil, which was used in the next step without purification. *m/z* = 320 (M+1).

Compound 126: To a stirring solution at room temperature under N_2 of compound **125** (entire amount from above, ≤ 1.51 mmol) and ethyl formate (13 mL, 161 mmol) in THF (20 mL) was added dropwise sodium methoxide (30 wt. % solution in methanol, 1.42 mL, 7.57 mmol). The sample was stirred overnight at room temperature then concentrated. Saturated aq. KH_2PO_4 solution (50 mL) was added and the mixture was extracted with $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give crude compound **126** (0.59 g) as yellow foamy solid, which was used in the next step without purification. *m/z* = 348 (M+1).

Compound 127 and 128: Crude compound **126** (entire amount from above, ≤ 1.51 mmol) and hydroxylamine hydrochloride (0.16 g, 2.30 mmol) in ethanol (25 mL) under N_2 was heated at 60 °C for 2 h, and then, stirred at room temperature overnight. The sample was concentrated then partitioned between saturated aq. $NaHCO_3$ solution (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give a mixture compound **127** and **128** (0.63 g) as tan foamy solid, which was used in the next step without purification. *m/z* = 345 (M+1 for **127**) and 363 (M+1 for **128**).

Compound 129 and 130: To a stirring solution at room temperature under N_2 of compound **127** and **128** (entire amount from above, ≤ 1.51 mmol) in methanol (30

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mL) was added dropwise sodium methoxide (30 wt.% solution in methanol, 1.7 mL, 9.1 mmol). The sample was stirred at room temperature overnight, concentrated then partitioned between saturated aq. KH_2PO_4 solution (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give a mixture compound **129** and **130** (0.57 g) as tan foamy solid, which was used in the next step without purification. *m/z* = 345 (M+1 for **129**) and 363 (M+1 for **130**).

Compounds T26 and T27: To a stirring solution at ~ 0 °C under N_2 of compound **127** and **128** (entire amount from above, ≤ 1.51 mmol) in DMF (6 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.26 g, 0.91 mmol) in DMF (4 mL). After stirring for 30 min, pyridine (1.5 mL, 18.5 mmol) was added, the ice-bath was removed and the sample was heated at 60 °C under N_2 for 4 h. The sample was cooled, concentrated then partitioned between saturated aq. KH_2PO_4 solution (50 mL) and $CHCl_3$ (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 50% EtOAc in hexanes) to give compound **T26** (84 mg, 16% yield from **124**) as a light yellow foamy solid and compound **T27** (69 mg, 13% yield from **124**) as a light yellow foamy solid. **T26**: *m/z* = 343 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.58 (m, 3H), 7.35 (m, 2H), 2.60 (m, 3H), 2.14 (m, 2H), 1.81 (m, 1H), 1.47 (s, 3H), 1.31 (d, 3H, *J* = 6.7 Hz). **T27**: m/z = 361 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.47 (m, 3H), 7.24 (m, 2H), 7.11 (br s, 1H), 5.28 (br s, 1H), 2.57 (qd, 1H, *J* = 6.8, 13.5 Hz), 2.42 (m, 2H), 2.12 (dt, 1H, *J* = 2.3, 12.7 Hz), 2.07 (m, 1H), 1.77 (tdd, 1H, *J* = 7.4, 10.2, 13.3 Hz), 1.46 (s, 3H), 1.29 (d, 3H, *J* = 6.7 Hz).

Compound T28: A solution of compound **T3** (35.8 mg, 0.108 mmol) and hydrido(dimethylphosphinous acid-kP)[hydrogen bis(dimethylphosphinito-kP)]platinum(II) (12.5 mg, 0.0291 mmol) in ethanol/water (4:1, 1 mL) was heated to 90 °C for 2 h. The crude mixture was concentrated to a solid, and the residue purified by column chromatography (silica gel, 0 to 100 % acetone in hexanes) to give compound **T28** (19 mg, 50 % yield) as a solid: *m/z* 350 (M+1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.42 (br s, 1H), 7.47 (m, 3H), 7.20 (dd, 2H, *J* = 1.8, 6.9 Hz), 5.55 (br s, 1H), 2.57 (qd, 1H, *J* = 6.8, 13.6 Hz), 2.44 (ddd, 1H, *J* = 6.4, 11.1, 17.2 Hz), 2.35 (dd,

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1H, J = 5.5, 16.7 Hz), 2.27 (s, 3H), 2.08 (dt, 1H, J = 2.2, 12.8 Hz), 1.99 (m, 1H), 1.74 (m, 1H), 1.43 (s, 3H), 1.27 (d, 3H, J = 6.8 Hz).

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All of the compounds, compositions, and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the disclosure may have focused on several embodiments or may have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations and modifications may be applied to the compounds, compositions, and methods without departing from the spirit, scope, and concept of the invention. All variations and modifications apparent to those skilled in the art are deemed to be within the spirit, scope, and concept of the invention as defined by the appended claims.

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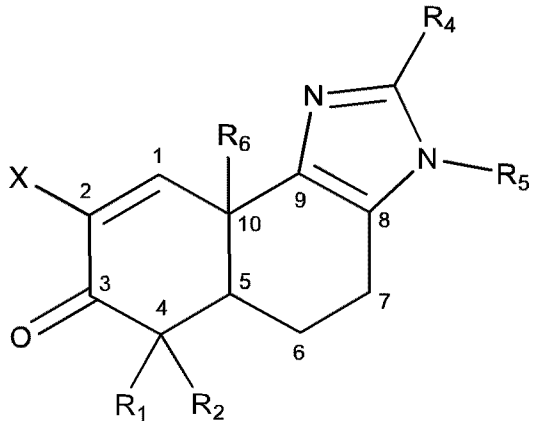
WHAT IS CLAIMED IS:

1. A compound of the formula:



,

wherein:

X is $-CN$ or $-C(O)R_a$, wherein R_a is $-NH_2$, alkylamino$_{(C\leq 6)}$, or dialkylamino$_{(C\leq 6)}$;

R_1 and R_2 are each independently hydrogen, alkyl$_{(C\leq 12)}$, or a substituted alkyl$_{(C\leq 12)}$;

R_4 is:

hydrogen, hydroxy, amino, halo, or cyano; 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$_{(C\leq 12)}$, heterocycloalkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, alkoxy$_{(C\leq 12)}$, aryloxy$_{(C\leq 12)}$, aralkoxy$_{(C\leq 12)}$, heteroaryloxy$_{(C\leq 12)}$, acyloxy$_{(C\leq 12)}$, alkylamino$_{(C\leq 12)}$, dialkylamino$_{(C\leq 12)}$, arylamino$_{(C\leq 12)}$, aralkylamino$_{(C\leq 12)}$, heteroarylamino$_{(C\leq 12)}$, amido$_{(C\leq 12)}$, or a substituted version of any of these groups; or

$-$alkanediyl$_{(C\leq 6)}-Y_1$, wherein Y_1 is:

hydroxy, amino, halo, or cyano; or

acyl$_{(C\leq 12)}$, alkoxy$_{(C\leq 12)}$, aryloxy$_{(C\leq 12)}$, aralkoxy$_{(C\leq 12)}$, heteroaryloxy$_{(C\leq 12)}$, acyloxy$_{(C\leq 12)}$, alkylamino$_{(C\leq 12)}$, dialkylamino$_{(C\leq 12)}$, arylamino$_{(C\leq 12)}$, aralkylamino$_{(C\leq 12)}$, heteroarylamino$_{(C\leq 12)}$, amido$_{(C\leq 12)}$, or a substituted version of any of these groups;

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R_5 is:

hydrogen or hydroxy; or

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

$-alkanediyl_{(C\leq6)}-Y_2$,

$-arenediyl_{(C\leq8)}-Y_3$, or

$-arenediyl_{(C\leq8)}-alkanediyl_{(C\leq6)}-Y_4$,

wherein Y_2, Y_3, and Y_4 are each independently:

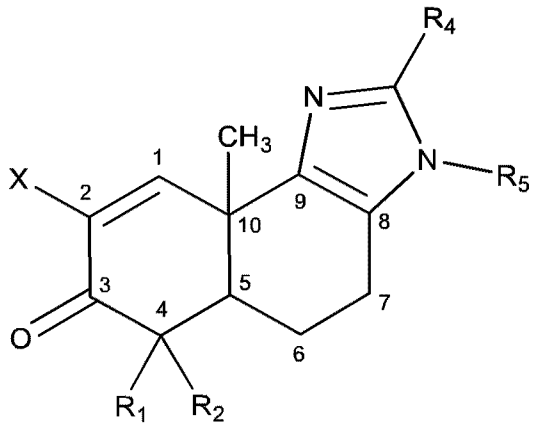
hydroxy, amino, halo, or cyano; or

$alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroaryl\text{-}amino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; and

R_6 is $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, further defined by the formula:



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wherein:

X is $-CN$ or $-C(O)R_a$, wherein R_a is $-NH_2$, $alkylamino_{(C\leq6)}$, or $dialkylamino_{(C\leq6)}$;

R_1 and R_2 are each independently hydrogen, $alkyl_{(C\leq12)}$, or a substituted $alkyl_{(C\leq12)}$;

R_4 is:

hydrogen, hydroxy, amino, halo, or cyano; or

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

$-alkanediyl_{(C\leq6)}-Y_1$, wherein Y_1 is:

hydroxy, amino, halo, or cyano; or

$acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; and

R_5 is:

hydrogen or hydroxy; or

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

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–alkanediyl$_{(C\leq6)}$–Y_2,

–arenediyl$_{(C\leq8)}$–Y_3, or

–arenediyl$_{(C\leq8)}$–alkanediyl$_{(C\leq6)}$–Y_4,

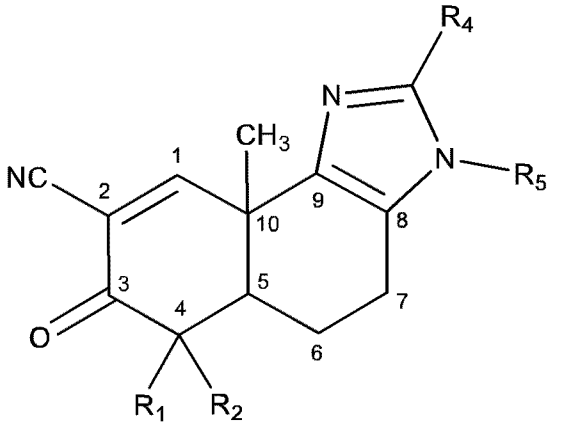
wherein Y_2, Y_3, and Y_4 are each independently:

hydroxy, amino, halo, or cyano; or

alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroaryl-amino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, further defined by the formula:



wherein:

R_1 and R_2 are each independently hydrogen, alkyl$_{(C\leq12)}$, or a substituted alkyl$_{(C\leq12)}$;

R_4 is:

hydrogen, hydroxy, amino, halo, or cyano; or

alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$,

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arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or

–alkanediyl$_{(C\leq6)}$–Y_1, wherein Y_1 is:

hydroxy, amino, halo, or cyano; or

acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; and

R_5 is:

hydrogen or hydroxy; or

alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or

–alkanediyl$_{(C\leq6)}$–Y_2,

–arenediyl$_{(C\leq8)}$–Y_3, or

–arenediyl$_{(C\leq8)}$–alkanediyl$_{(C\leq6)}$–Y_4,

wherein Y_2, Y_3, and Y_4 are each independently:

hydroxy, amino, halo, or cyano; or

alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroaryl-amino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt thereof.

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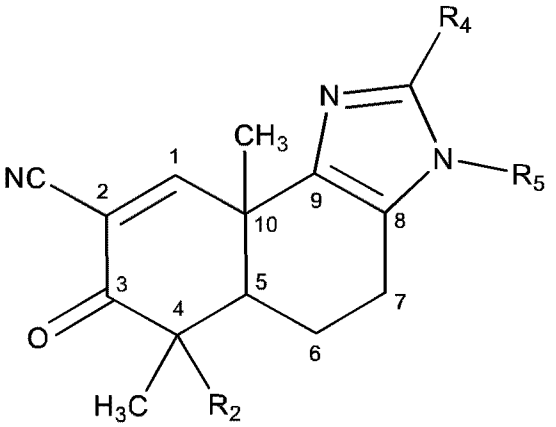
4. The compound of claim 3, further defined by the formula:



,

wherein:

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

R_4 is:

hydrogen, hydroxy, amino, halo, or cyano; or

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

$-alkanediyl_{(C\leq6)}-Y_1$, wherein Y_1 is:

hydroxy, amino, halo, or cyano; or

$acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; and

R_5 is:

hydrogen or hydroxy; or

$alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$,

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alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or

–alkanediyl$_{(C\leq6)}$–Y_2,

–arenediyl$_{(C\leq8)}$–Y_3, or

–arenediyl$_{(C\leq8)}$–alkanediyl$_{(C\leq6)}$–Y_4,

wherein Y_2, Y_3, and Y_4 are each independently:

hydroxy, amino, halo, or cyano; or

alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroaryl-amino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1-4, wherein:

R_4 is:

hydrogen, hydroxy, amino, halo, or cyano; or

alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; and

R_5 is:

hydrogen or hydroxy; or

alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$,

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arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups.

6. The compound according to any one of claims 1-4, wherein:

R_4 is hydroxy, amino, halo, cyano, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, or amido$_{(C\leq12)}$; and

R_5 is hydrogen, hydroxy, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, or amido$_{(C\leq12)}$.

7. The compound of claim 1 or 2, wherein X is cyano.

8. The compound of claim 1 or 2, wherein X is $-C(O)R_a$, wherein R_a is $-NH_2$.

9. The compound according to any one of claims 1-3, wherein R_1 is hydrogen.

10. The compound according to any one of claims 1-3, wherein R_1 is alkyl$_{(C\leq12)}$.

11. The compound according to any one of claims 1-3, wherein R_1 is methyl.

12. The compound according to any one of claims 1-3, wherein R_2 is hydrogen.

13. The compound according to any one of claims 1-4 or 7-12, wherein R_4 is halo or cyano; alkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, or a substituted version of any of these groups; or $-$alkanediyl$_{(C\leq6)}-Y_1$, wherein Y_1 is: aralkoxy$_{(C\leq12)}$ or a substituted aralkoxy$_{(C\leq12)}$.

14. The compound of claim 13, wherein R_4 is cyano.

15. The compound of claims 13, wherein R_4 is halo.

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16. The compound of claim 15, wherein R_4 is bromo.

17. The compound of claim 13, wherein R_4 is substituted $acyl_{(C\leq12)}$.

18. The compound of claim 17, wherein R_4 is $-C(O)NH_2$.

19. The compound of claim 13, wherein R_4 is $alkyl_{(C\leq12)}$.

20. The compound of claim 19, wherein R_4 is methyl.

21. The compound of claim 13, wherein R_4 is substituted $alkyl_{(C\leq12)}$.

22. The compound of claim 21, wherein R_4 is 2-hydroxyethyl.

23. The compound of claim 13, wherein R_4 is $aryl_{(C\leq12)}$.

24. The compound of claim 23, wherein R_4 is phenyl or 2-methylphenyl.

25. The compound of claim 13, wherein R_4 is $heteroaryl_{(C\leq12)}$.

26. The compound of claim 25, wherein R_4 is 4-pyridyl or 4-(1-methyl)pyrazolyl.

27. The compound according to any one of claims 1-4 and 7-13, wherein R_4 is $-alkanediyl_{(C\leq6)}-Y_1$.

28. The compound of claim 27, wherein the $alkanediyl_{(C\leq6)}$ is $-CH_2CH_2-$.

29. The compound of either claim 27 or 28, wherein Y_1 is hydroxy or $aralkoxy_{(C\leq12)}$.

30. The compound of claim 29, wherein Y_1 is $-OCH_2C_6H_5$.

31. The compound according to any one of claims 1-4 and 7-30, wherein R_5 is hydrogen; $alkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, or a substituted version of any of these groups; or $-arenediyl_{(C\leq8)}-Y_3$, wherein Y_3 is: $heteroaryl_{C\leq12}$ or a substituted $heteroaryl_{(C\leq12)}$.

32. The compound according to any one of claims 1-31, wherein R_5 is hydrogen.

33. The compound according to any one of claims 1-31, wherein R_5 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$.

34. The compound of claim 33, wherein R_5 is $-CH_2CH_2CH_2OCH_3$.

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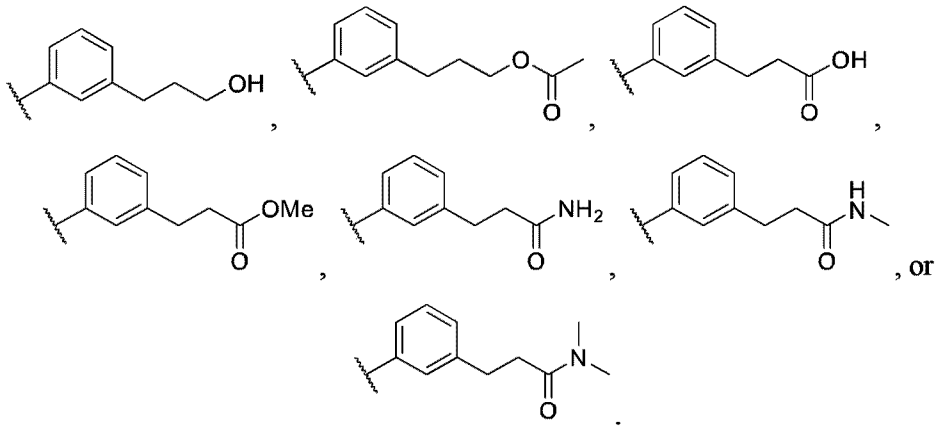
35. The compound according to any one of claims 1-31, wherein R_5 is $aryl_{(C\leq12)}$.

36. The compound of claim 35, wherein R_5 is phenyl, 2-methylphenyl, 1,1′-biphenyl-3-yl, or 1,1′-biphenyl-4-yl.

37. The compound according to any one of claims 1-31, wherein R_5 is substituted $aryl_{(C\leq12)}$.

38. The compound of claim 37, wherein R_5 is



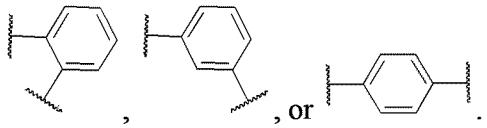
, or .

39. The compound according to any one of claims 1-31, wherein R_5 is $heteroaryl_{(C\leq12)}$.

40. The compound of claim 39, wherein R_5 is 4-(1-methyl)pyrazolyl or 5-(2-methyl)tetrazolyl.

41. The compound according to any one of claims 1-4 and 7-31, wherein R_5 is $-arenediyl_{(C\leq8)}-Y_3$.

42. The compound of claim 41, wherein the $arenediyl_{(C\leq8)}$ is:



, , or .

43. The compound of either claim 41 or 42, wherein Y_3 is $heteroaryl_{(C\leq12)}$.

44. The compound of claim 43, wherein Y_3 is 5-pyrimidinyl.

45. The compound of claim 1, wherein R_6 is methyl.

46. The compound of claim 1, wherein R_6 is phenyl.

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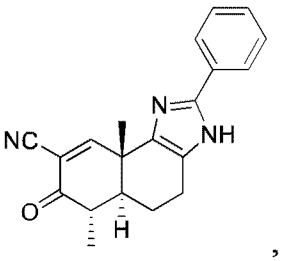
47. The compound according to any one of claims 1-46, wherein the carbon atom labeled 4 is in the *S* configuration.

48. The compound according to any one of claims 1-47, wherein the carbon atom labeled 5 is in the *S* configuration.

49. The compound according to any one of claims 1-48, wherein the carbon atom labeled 10 is in the *R* configuration.

50. A compound selected from: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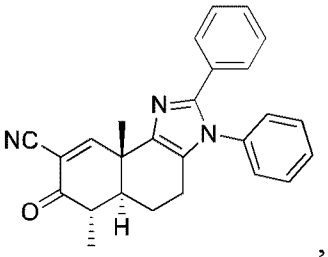
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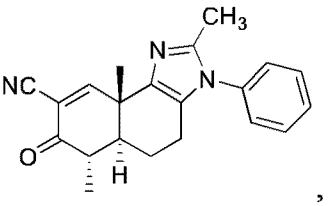
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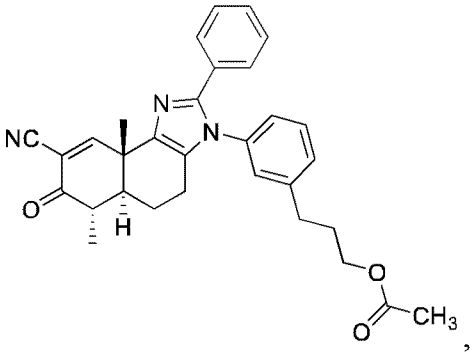
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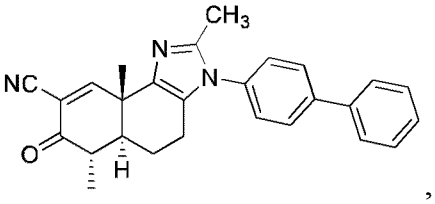
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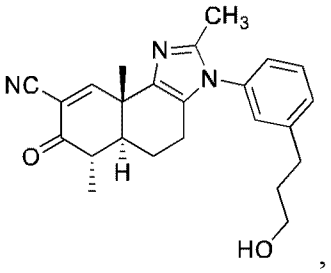
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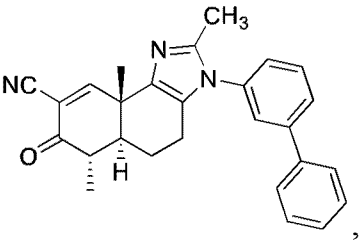
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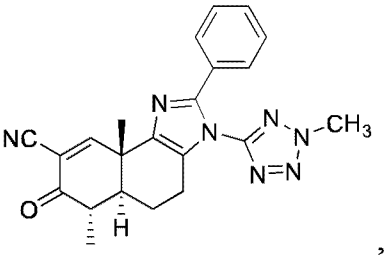
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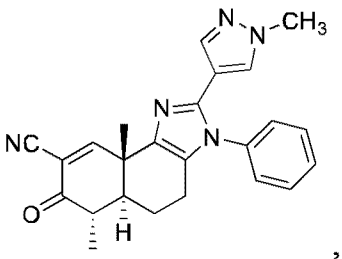
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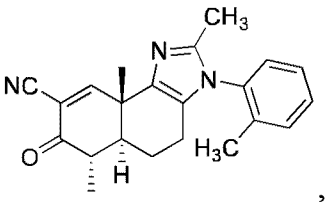
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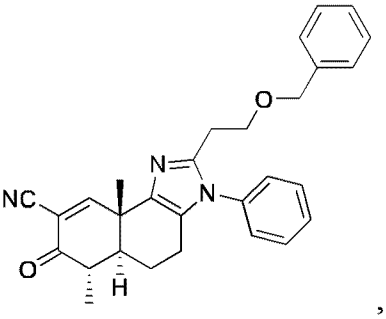
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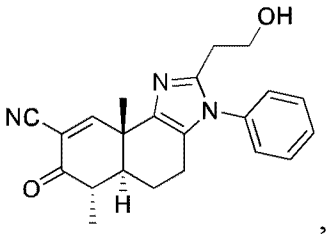
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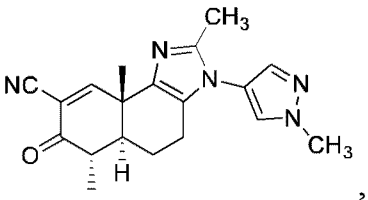
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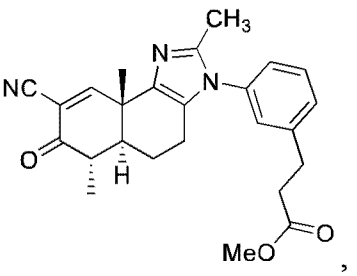
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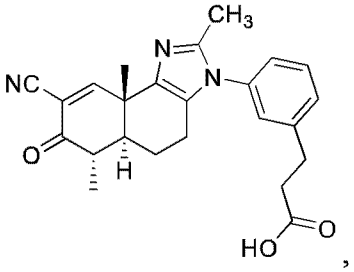
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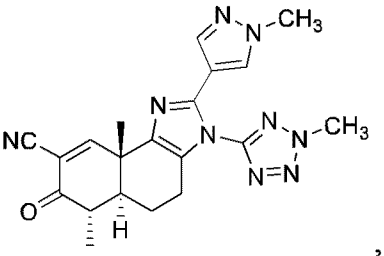
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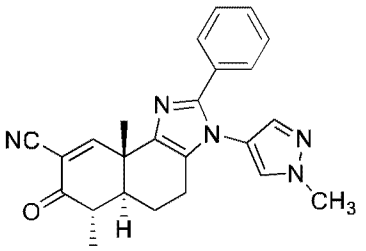
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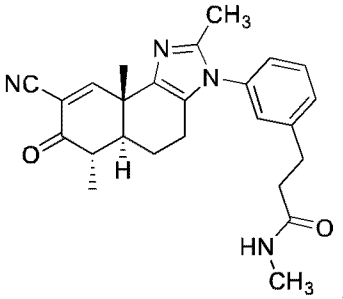
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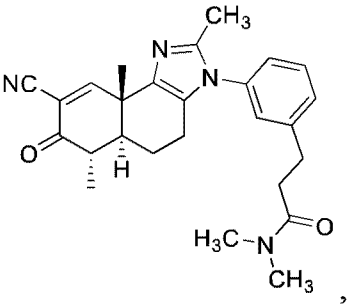
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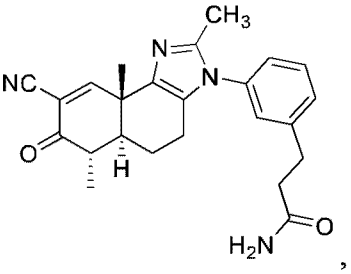
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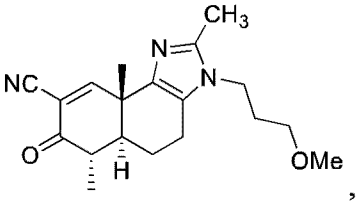
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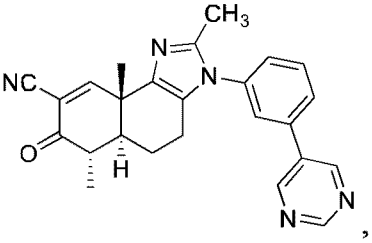
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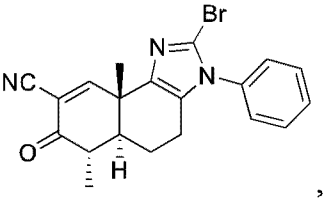
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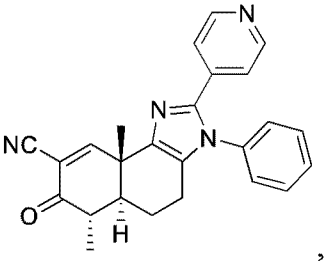
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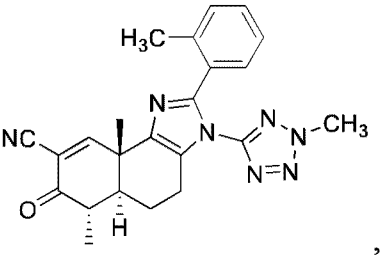
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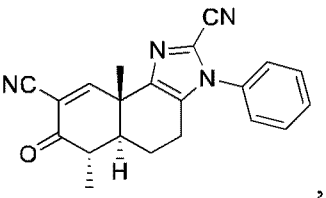
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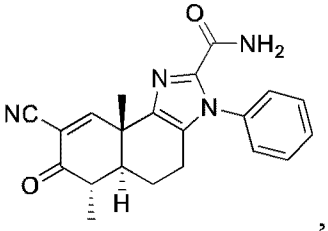
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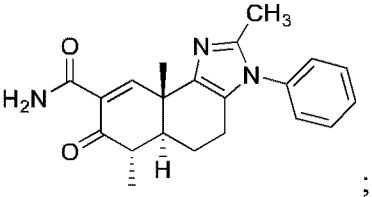
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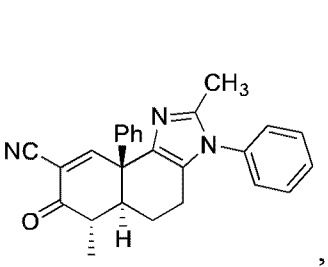
or a pharmaceutically acceptable salt of any of the above formulas.

51. A compound selected from:



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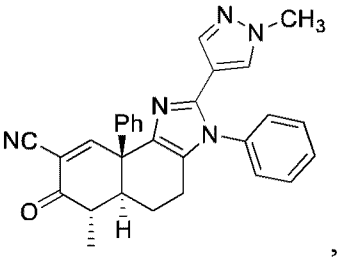

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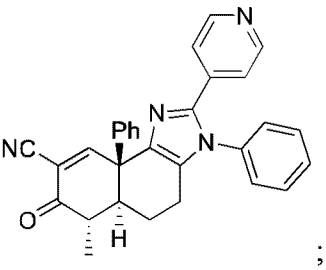

;

or a pharmaceutically acceptable salt of any of the above formulas.

52. A pharmaceutical composition comprising:

a) a compound according to any one of claims 1-51; and

b) an excipient.

53. Use of a compound of any one of claims 1-51 or the composition of claim 52 for the treatment or prevention of a disease or disorder in a patient.

54. The use of claim 53, wherein the patient is a human, primate, horse, cow, sheep, goat, guinea pig, dog, cat, rat, or mouse.

55. The use of claim 54, wherein the patient is a human.

56. The use of claim 53, where in the disease or disorder is associated with inflammation.

57. The use of claim 53, wherein the disease or disorder is characterized by overexpression of iNOS genes in the patient.

58. The use of claim 53, wherein the disease or disorder is characterized by overexpression of COX-2 genes in the patient.

59. Use of a compound of any one of claims 1-51 or the composition of claim 52 for inhibiting IFN-γ-induced nitric oxide production in one or more cells of a patient.

60. Use of a compound of any one of claims 1-51 or the composition of claim 52 for preparation of a medicament for the treatment or prevention of a disease or disorder in

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a patient, wherein the the disease or disorder is associated with inflammation, is characterized by overexpression of iNOS genes in the patient or is characterized by overexpression of COX-2 genes in the patient.

61. The use of claim 60, wherein the patient is a human, primate, horse, cow, sheep, goat, guinea pig, dog, cat, rat, or mouse.

62. The use of claim 61, wherein the patient is a human.

63. Use of a compound of any one of claism 1-51 or the composition of claim 52 for preparation of a medicament for inhibiting IFN-γ-induced nitric oxide production in one or more cells of a patient.

64. A compound of any one of claims 1-51 or the composition of claim 52 for use to treat or prevent a disease or disorder in a patient, wherein the the disease or disorder is associated with inflammation, is characterized by overexpression of iNOS genes in the patient or is characterized by overexpression of COX-2 genes in the patient.

65. The compound of composition for use of claim 64, wherein the patient is a human, primate, horse, cow, sheep, goat, guinea pig, dog, cat, rat, or mouse.

66. The compound of composition for use of claim 65, wherein the patient is a human.

67. A compound of any one of claims 1-51 or the composition of claim 52 for use to inhibit IFN-γ-induced nitric oxide production in one or more cells of a patient.

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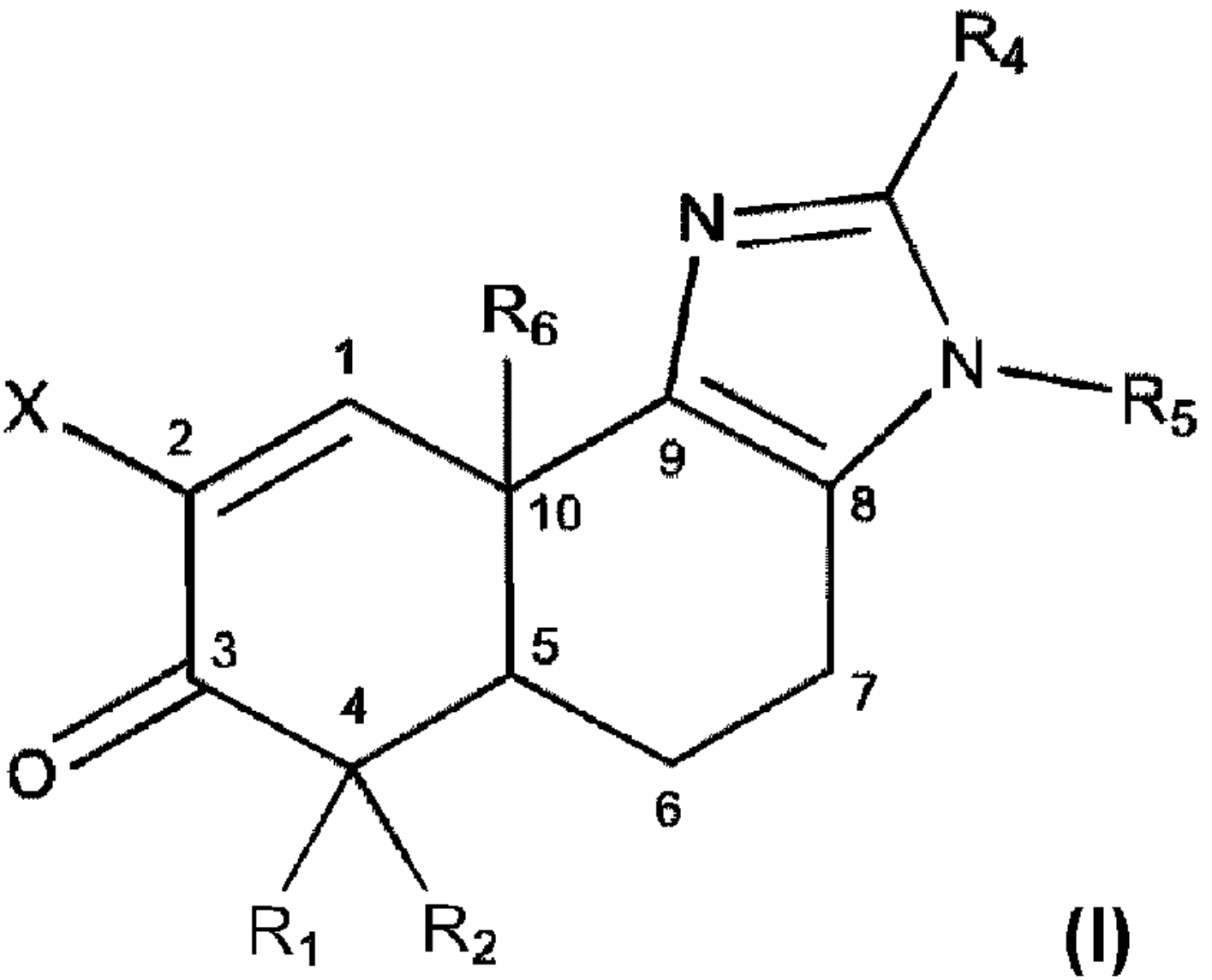

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