

DESCRIPTION

PYRAZOLYL AND PYRIMIDINYL TRICYCLIC ENONES AS ANTIOXIDANT INFLAMMATION MODULATORS

BACKGROUND OF THE INVENTION

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The present application claims the benefit of priority to U.S. Provisional Application 61/424,601, filed Dec. 17, 2010, the contents of which are incorporated herein by reference.

I. Field of the Invention

10 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

15 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-diooxoleana-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.*,
20 1998; Suh *et al.*, 1999; Place *et al.*, 2003; Liby *et al.*, 2005). The methyl ester, bardoxolone-methyl (CDDO-Me), is currently being evaluated in phase II clinical trials for the treatment of diabetic nephropathy and chronic kidney disease.

Synthetic triterpenoid analogs of oleanolic acid have also been shown to be inhibitors of cellular inflammatory processes, such as the induction by IFN- γ of
25 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), which are all incorporated herein by reference. Synthetic derivatives of another triterpenoid, betulinic acid, have also been shown to inhibit cellular inflammatory processes, although these compounds have been less extensively characterized (Honda *et al.*,
30 2006). The pharmacology of these synthetic triterpenoid molecules is complex. Compounds derived from oleanolic acid have 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 (e.g., Dinkova-Kostova *et al.*, 2005; Ahmad *et al.*, 2006; Ahmad *et al.*, 2008; Liby *et al.*, 2007a). Derivatives of betulinic acid, though they have shown comparable anti-inflammatory properties, also appear to have significant differences in their pharmacology compared to OA-derived compounds (Liby *et al.*, 2007b).

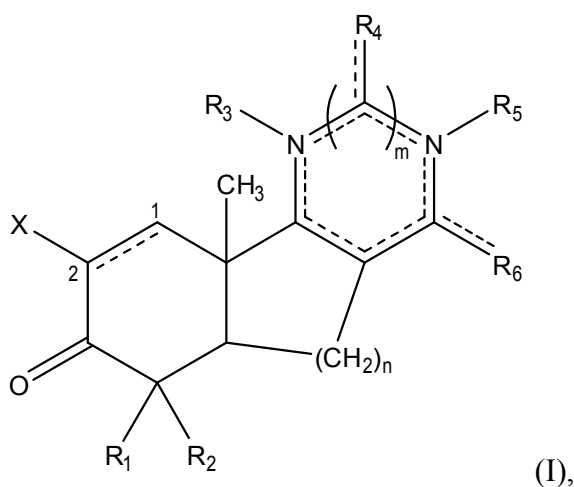
In general, it is not certain that the triterpenoid starting materials employed to date have optimal properties for all applications compared to other possible starting materials. In addition, it is often necessary to synthesize triterpenoid derivatives from natural product starting materials. The production of highly purified triterpenoid starting materials can be expensive, and the plant materials that are the ultimate sources of these compounds can vary in availability, including due to adverse weather conditions, disease, and other environmental factors. Given that the biological activity profiles of known triterpenoid derivatives vary, and in view of the wide variety of diseases that may be treated or prevented with compounds having potent antioxidant and anti-inflammatory effects, and the high degree of unmet medical need represented within this variety of diseases, it is desirable to synthesize new compounds with diverse structures that may have improved biological activity profiles for the treatment of one or more indications. Therefore, the design of potent, selective antioxidant/anti-inflammatory compounds that can be readily synthesized from simple starting materials is a desirable goal.

SUMMARY

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

The present invention refers to subject matter as defined in the attached set of claims.

In one example of the present disclosure there are disclosed compounds of the formula:



wherein:

the atoms labeled 1 and 2 are connected either by a double bond or an epoxidized double bond;

n is 1 or 2;

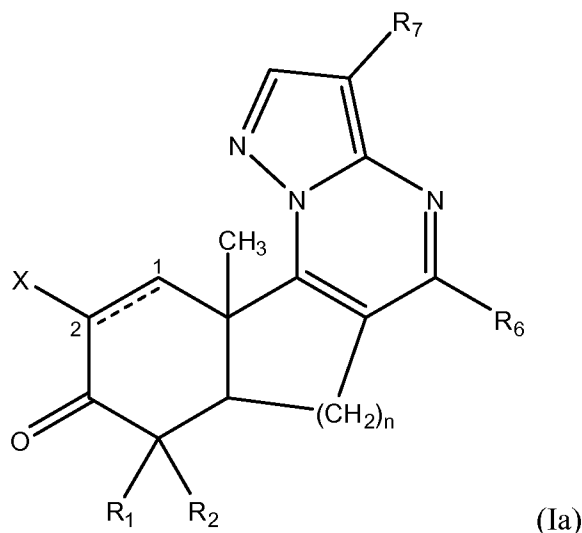
m is 0 or 1;

X is $-\text{CN}$, $-\text{CF}_3$, or $-\text{C}(\text{O})\text{R}_a$, wherein R_a is $-\text{OH}$, $\text{alkoxy}_{(\text{C}\leq 6)}$, $\text{alkylamino}_{(\text{C}\leq 6)}$, $\text{dialkylamino}_{(\text{C}\leq 6)}$, or $-\text{NHS}(\text{O})_2\text{-alkyl}_{(\text{C}1-4)}$;

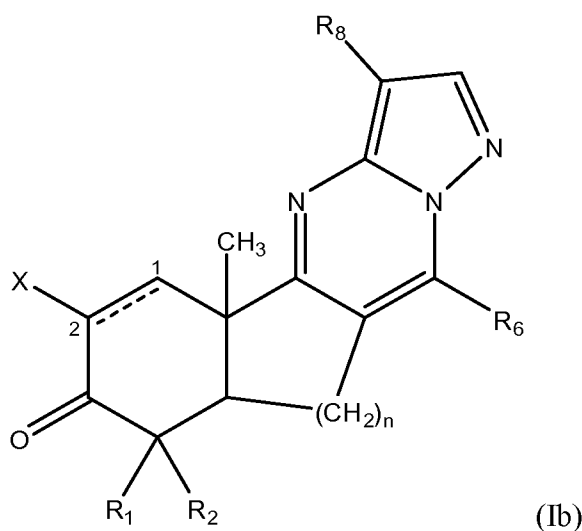
R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{alkenyl}_{(\text{C}\leq 12)}$, $\text{alkynyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$, $\text{aralkyl}_{(\text{C}\leq 12)}$, $\text{heteroaryl}_{(\text{C}\leq 12)}$, $\text{heterocycloalkyl}_{(\text{C}\leq 12)}$, $\text{acyl}_{(\text{C}\leq 12)}$, $\text{alkoxy}_{(\text{C}\leq 12)}$, $\text{aryloxy}_{(\text{C}\leq 12)}$, $\text{aralkoxy}_{(\text{C}\leq 12)}$, $\text{heteroaryloxy}_{(\text{C}\leq 12)}$, $\text{acyloxy}_{(\text{C}\leq 12)}$, $\text{alkylamino}_{(\text{C}\leq 12)}$, $\text{dialkylamino}_{(\text{C}\leq 12)}$, $\text{aryl amino}_{(\text{C}\leq 12)}$, $\text{aralkylamino}_{(\text{C}\leq 12)}$, $\text{heteroaryl amino}_{(\text{C}\leq 12)}$, $\text{amido}_{(\text{C}\leq 12)}$, or a substituted version of any of these groups; or

- R_1 and R_2 are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkoxydiyl_(C≤12), alkylaminodiyl_(C≤12), or a substituted version of any of these groups;
- 5 R_3 is absent, hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups; or R_3 is taken together with R_4 as provided below; provided that R_3 is absent when and only when the atom to which it is bound forms part of a double bond;
- 10 R_4 is hydrogen, hydroxy, amino, halo, cyano, or oxo; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups; or R_4 is
- 15 taken together with either R_3 or R_5 as provided below;
- R_5 is absent, hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups; or R_5 is taken together with R_4 as provided below; provided that R_5 is absent when and only when
- 20 the atom to which it is bound forms part of a double bond; and
- R_6 is hydrogen, hydroxy, amino, halo, cyano, or oxo; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkyl-
- 25 amino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

provided that when R₃ and R₄ are taken together, the compound is further defined by formula Ia:



wherein R₇ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12),
 5 alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12),
 heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralk-
 oxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkyl-
 amino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12),
 amido_(C≤12), or a substituted version of any of these groups; or
 10 provided that when R₄ and R₅ are taken together, the compound is further
 defined by formula Ib:

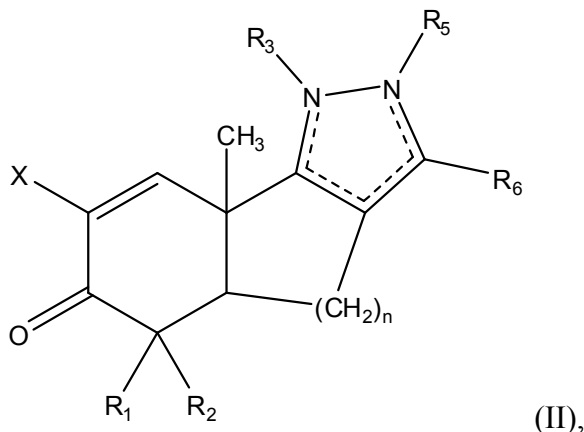


wherein R₈ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12),
 alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12),
 15 heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralk-

oxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

5 In some examples, the compounds are further defined by the formula:



wherein:

n is 1 or 2;

X is -CN, -CF₃, or -C(O)R_a, wherein R_a is -OH, alkoxy_(C≤6), alkylamino_(C≤6),
10 dialkylamino_(C≤6), or -NHS(O)₂-alkyl_(C1-4);

R₁ and R₂ are each independently hydrogen, hydroxy, halo, or amino; or
alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), hetero-
aryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12),
aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12),
15 dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroaryl-
amino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;
or

R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12),
alkoxydiyl_(C≤12), alkylaminodiyl_(C≤12), or a substituted version of any of
20 these groups;

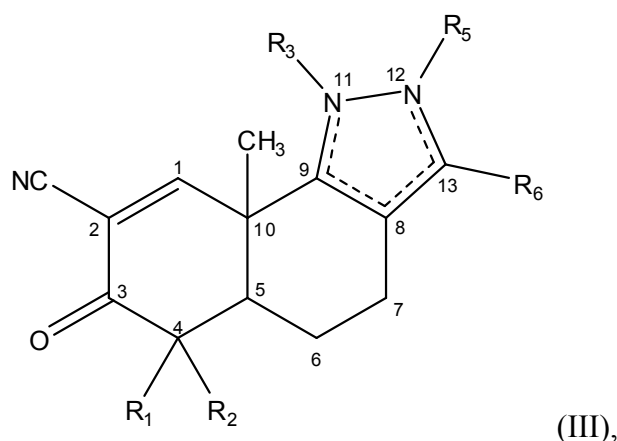
R₃ is absent, hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a
substituted version of any of these groups; provided that R₃ is absent
when and only when the atom to which it is bound forms part of a
25 double bond;

R₅ is absent, hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups; provided that R₅ is absent when and only when the atom to which it is bound forms part of a double bond; and

R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, the compounds are further defined by the formula:



wherein:

R₁ and R₂ are each independently hydrogen, hydroxy, halo, or amino; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups; or

R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkoxydiyl_(C≤12), alkylaminodiyl_(C≤12), or a substituted version of any of these groups;

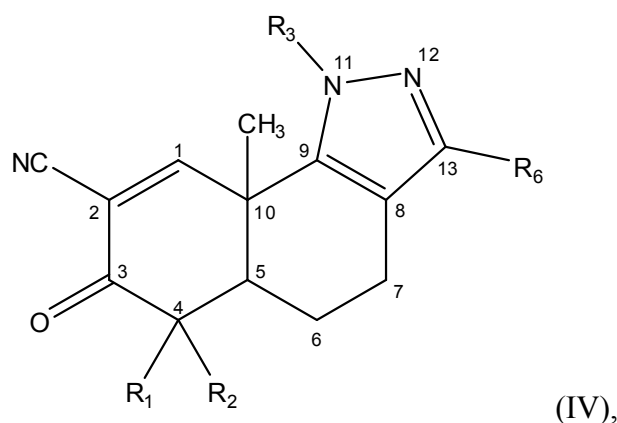
R₃ is absent, hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups; provided that R₃ is absent when and only when the atom to which it is bound forms part of a double bond;

R₅ is absent, hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups; provided that R₅ is absent when and only when the atom to which it is bound forms part of a double bond; and

R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, the compounds are further defined by the formula:



wherein:

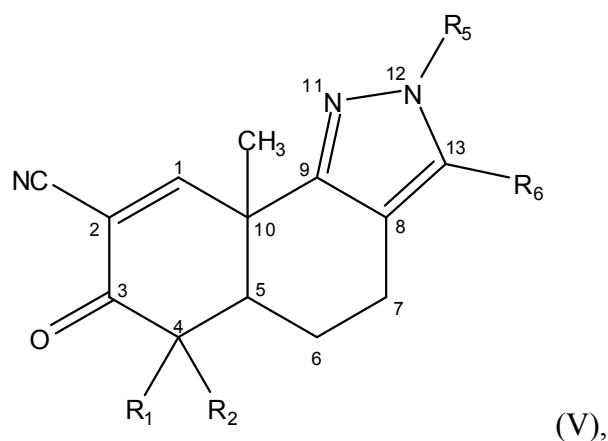
R₁ and R₂ are each independently hydrogen, hydroxy, halo, or amino; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

R₃ is hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups; and

5 R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

10 or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, the compounds are further defined by the formula:



wherein:

15 R₁ and R₂ are each independently hydrogen, hydroxy, halo, or amino; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;
20 or

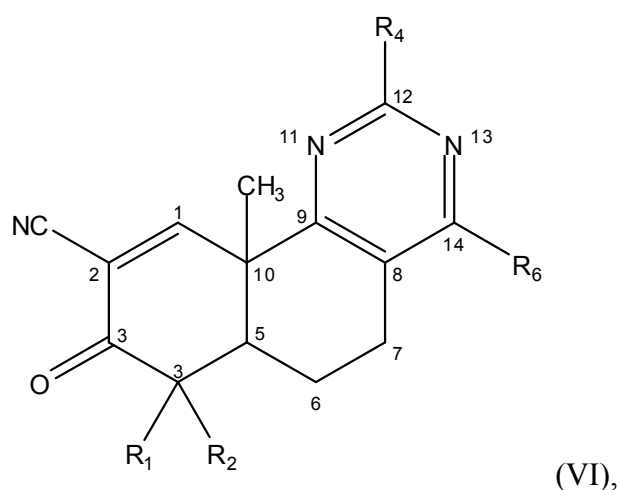
R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), alkoxydiyl_(C≤12), alkylaminodiyl_(C≤12), or a substituted version of any of these groups;

R₅ is hydrogen; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups; and

5 R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

10 or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, the compounds are further defined by the formula:



wherein:

15 R₁ and R₂ are each independently hydrogen, hydroxy, halo, or amino; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups;

20 R₄ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12),

arylamino_(C≤12), aralkylamino_(C≤12), heteroaryl_(C≤12), amido_(C≤12),
 or a substituted version of any of these groups;

5 R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12),
 alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocyclo-
 alkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryloxy_(C≤12), aralkoxy_(C≤12),
 heteroaryloxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12),
 arylamino_(C≤12), aralkylamino_(C≤12), heteroaryl_(C≤12), amido_(C≤12),
 or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

10 In some examples, the atoms labeled 1 and 2 are connected by a double bond.
 In some examples, the atoms labeled 1 and 2 are connected by an epoxidized double
 bond. In some examples, n is 1. In some examples, n is 2. In some examples, m is 0.
 In some examples, m is 1. In some examples, X is –CN. In some examples, X is –
 CF₃. In some examples, X is hydrogen.

15 In some examples, R₁ or R₂ is alkyl_(C≤8) or substituted alkyl_(C≤8). In some
 examples, R₁ or R₂ is alkyl_(C≤8). In some examples, R₁ or R₂ is methyl. In some
 examples, R₁ and R₂ are each methyl. In some examples, R₁ is methyl and R₂ is
 hydrogen. In some examples, R₁ or R₂ is ethyl. In some examples, R₁ is ethyl and R₂
 is hydrogen. In some examples, R₁ or R₂ is hydrogen. In some examples, R₁ and R₂

20 are each hydrogen. In some examples, R₁ and R₂ are taken together and are
 alkanediyl_(C≤8). In some examples, R₁ and R₂ are taken together and are 1,4-
 butanediyl. In some examples, R₁ or R₂ is aryl_(C≤8). In some examples, R₁ or R₂ is
 phenyl. In some examples, R₁ is phenyl and R₂ is hydrogen. In some examples, R₁ or
 R₂ is aralkyl_(C≤8). In some examples, R₁ or R₂ is benzyl. In some examples, R₁ is

25 benzyl and R₂ is hydrogen. In some examples, R₁ and R₂ are each benzyl.

In some examples, R₃ is absent. In some examples, R₃ is hydrogen. In some
 examples, R₃ is alkyl_(C≤8), aryl_(C≤8), acyl_(C≤8), alkoxy_(C≤8) or a substituted version of any
 of these groups. In some examples, R₃ is alkyl_(C≤4) or substituted alkyl_(C≤4). In some
 examples, R₃ is alkyl_(C≤4). In some examples, R₃ is methyl. In some examples, R₃ is

30 aryl_(C≤8) or substituted aryl_(C≤8). In some examples, R₃ is aryl_(C≤8). In some examples,
 R₃ is phenyl.

In some examples, R₄ is hydrogen. In some examples, R₄ is oxo. In some examples, R₄ is alkyl_(C≤8), aryl_(C≤8), acyl_(C≤8), alkoxy_(C≤8) or a substituted version of any of these groups. In some examples, R₄ is alkyl_(C≤6) or substituted alkyl_(C≤6). In some examples, R₄ is alkyl_(C≤6). In some examples, R₄ is methyl, isopropyl, *t*-butyl, or cyclopropyl. In some examples, R₄ is haloalkyl_(C≤6). In some examples, R₄ is trifluoromethyl. In some examples, R₄ is alkoxy_(C≤6). In some examples, R₄ is methoxy or ethoxy. In some examples, R₄ is aryl_(C≤8) or substituted aryl_(C≤8). In some examples, R₄ is phenyl, chlorophenyl, methylphenyl, or methoxyphenyl. In some examples, R₄ is heteroaryl_(C≤8). In some examples, R₄ is pyridinyl or pyrimidinyl. In some examples, R₄ is acyl_(C≤6) or substituted acyl_(C≤6). In some examples, R₄ is ethoxycarbonyl.

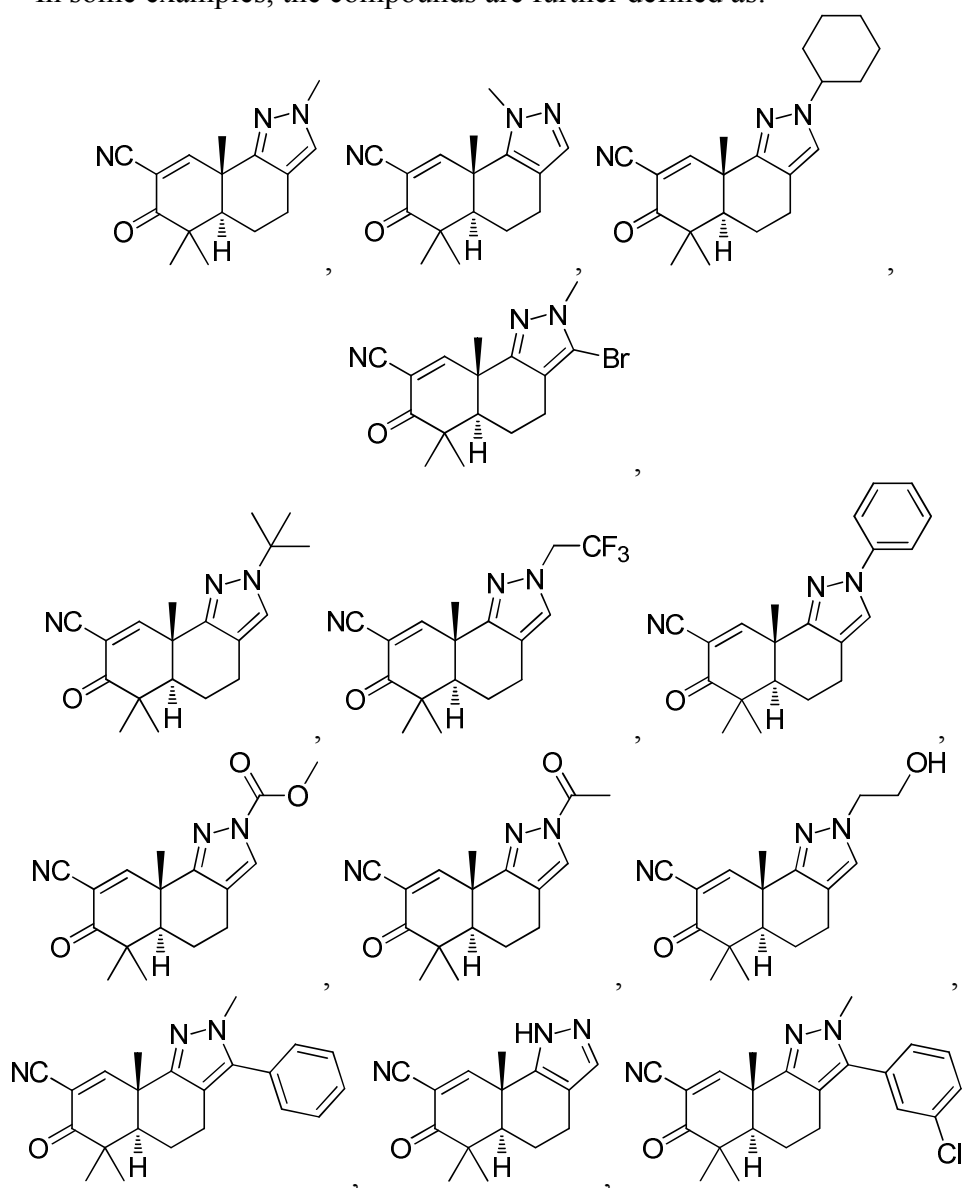
In some examples, R₅ is absent. In some examples, R₅ is hydrogen. In some examples, R₅ is alkyl_(C≤8), aryl_(C≤8), acyl_(C≤8), alkoxy_(C≤8) or a substituted version of any of these groups. In some examples, R₅ is alkyl_(C≤6) or substituted alkyl_(C≤6). In some examples, R₅ is alkyl_(C≤6). In some examples, R₅ is methyl, cyclohexyl, or *t*-butyl. In some examples, R₅ is substituted alkyl_(C≤4). In some examples, R₅ is 2-hydroxyethyl or 2,2,2-trifluoroethyl. In some examples, R₅ is aryl_(C≤8) or substituted aryl_(C≤8). In some examples, R₅ is aryl_(C≤8). In some examples, R₅ is phenyl. In some examples, R₅ is acyl_(C≤8) or substituted acyl_(C≤8). In some examples, R₅ is acetyl, methoxycarbonyl, ethoxycarbonyl, or phenylcarbonyl.

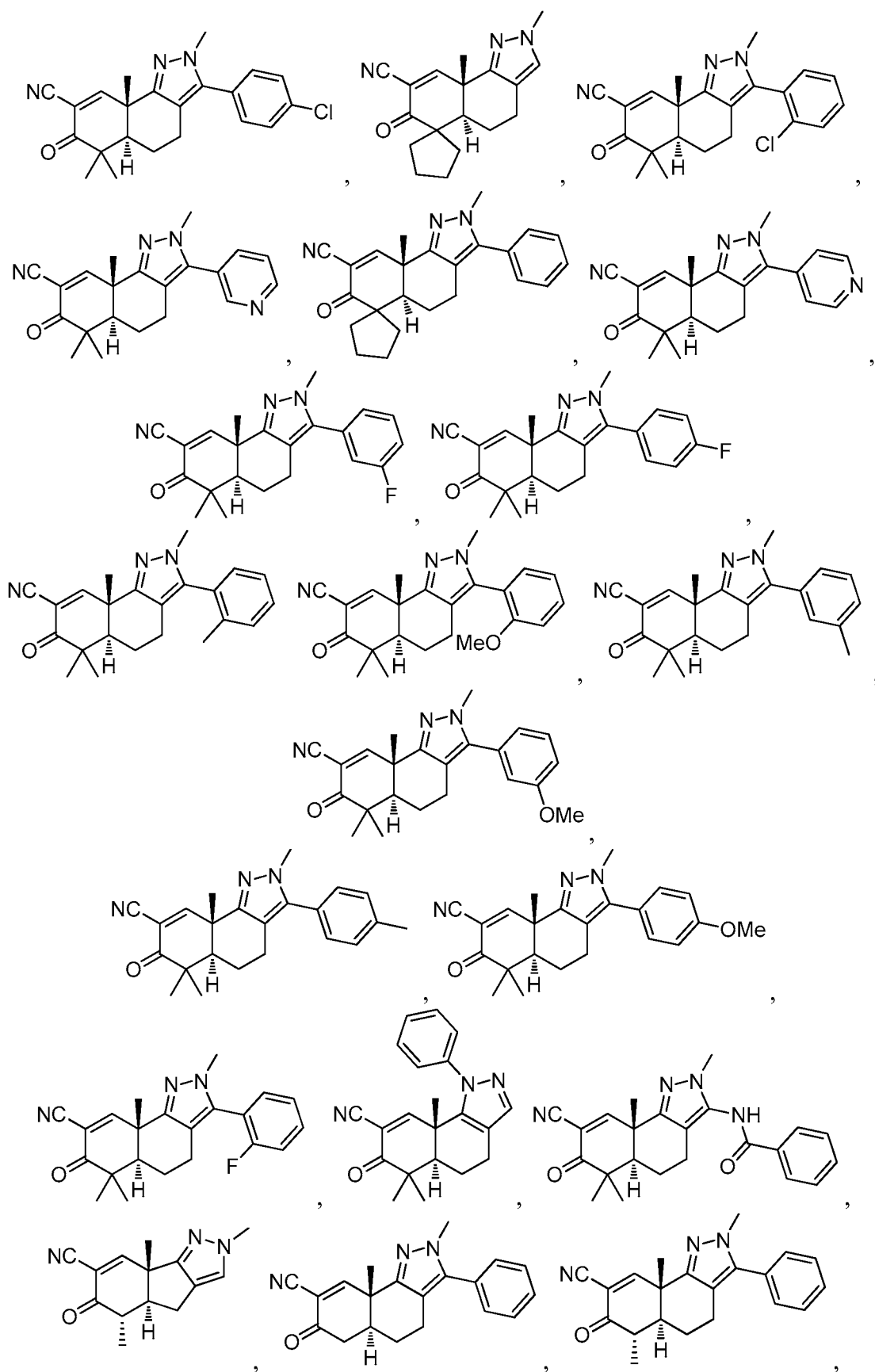
In some examples, R₆ is hydrogen. In some examples, R₆ is cyano. In some examples, R₆ is halo. In some examples, R₆ is chloro or bromo. In some examples, R₆ is alkyl_(C≤6) or substituted alkyl_(C≤6). In some examples, R₆ is alkyl_(C≤6). In some examples, R₆ is methyl, isopropyl or cyclohexyl. In some examples, R₆ is aryl_(C≤8), heteroaryl_(C≤8) or a substituted version of either of these groups. In some examples, R₆ is aryl_(C≤10). In some examples, R₆ is phenyl, methylphenyl or naphthyl. In some examples, R₆ is substituted aryl_(C≤8). In some examples, R₆ is chlorophenyl, fluorophenyl or methoxyphenyl. In some examples, R₆ is heteroaryl_(C≤8). In some examples, R₆ is pyridinyl, pyrimidinyl, methylpyrazolyl, dimethylisoxazolyl, methyltriazolyl, or methyltetrazolyl. In some examples, R₆ is aralkyl_(C≤12) or substituted aralkyl_(C≤12).

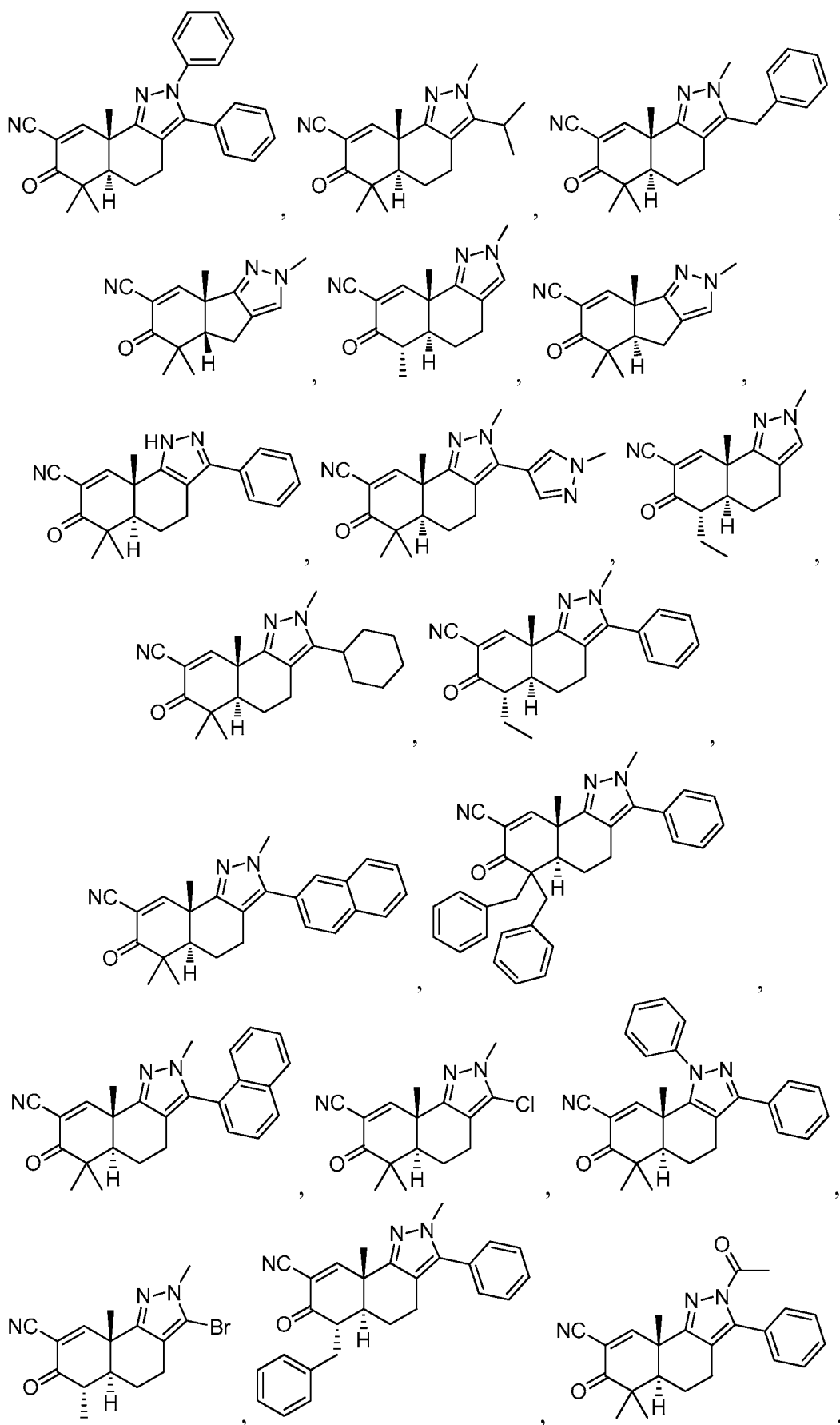
In some examples, R₆ is benzyl. In some examples, R₆ is amido_(C≤8). In some examples, R₆ is phenylcarbonylamino. In some examples, R₆ is alkynyl_(C≤8). In some examples, R₆ is ethynyl. In some examples, R₆ is acyl_(C≤8). In some examples, R₆ is aminocarbonyl or dimethylaminocarbonyl. In some examples, R₆ is alkoxy_(C≤8). In some examples, R₆ is methoxy. In some examples, carbon atom 10 is in the *R* configuration. In some examples, carbon atom 10 is in the *S* configuration. In some examples, carbon atom 5 is in the *R* configuration. In some examples, carbon atom 5 is in the *S* configuration.

In some examples, R₇ or R₈ is hydrogen. In some examples, R₇ or R₈ is halo. In some examples, R₇ or R₈ is bromo. In some examples, R₇ or R₈ is aryl_(C≤8). In some examples, R₇ or R₈ is phenyl.

In some examples, the compounds are further defined as:

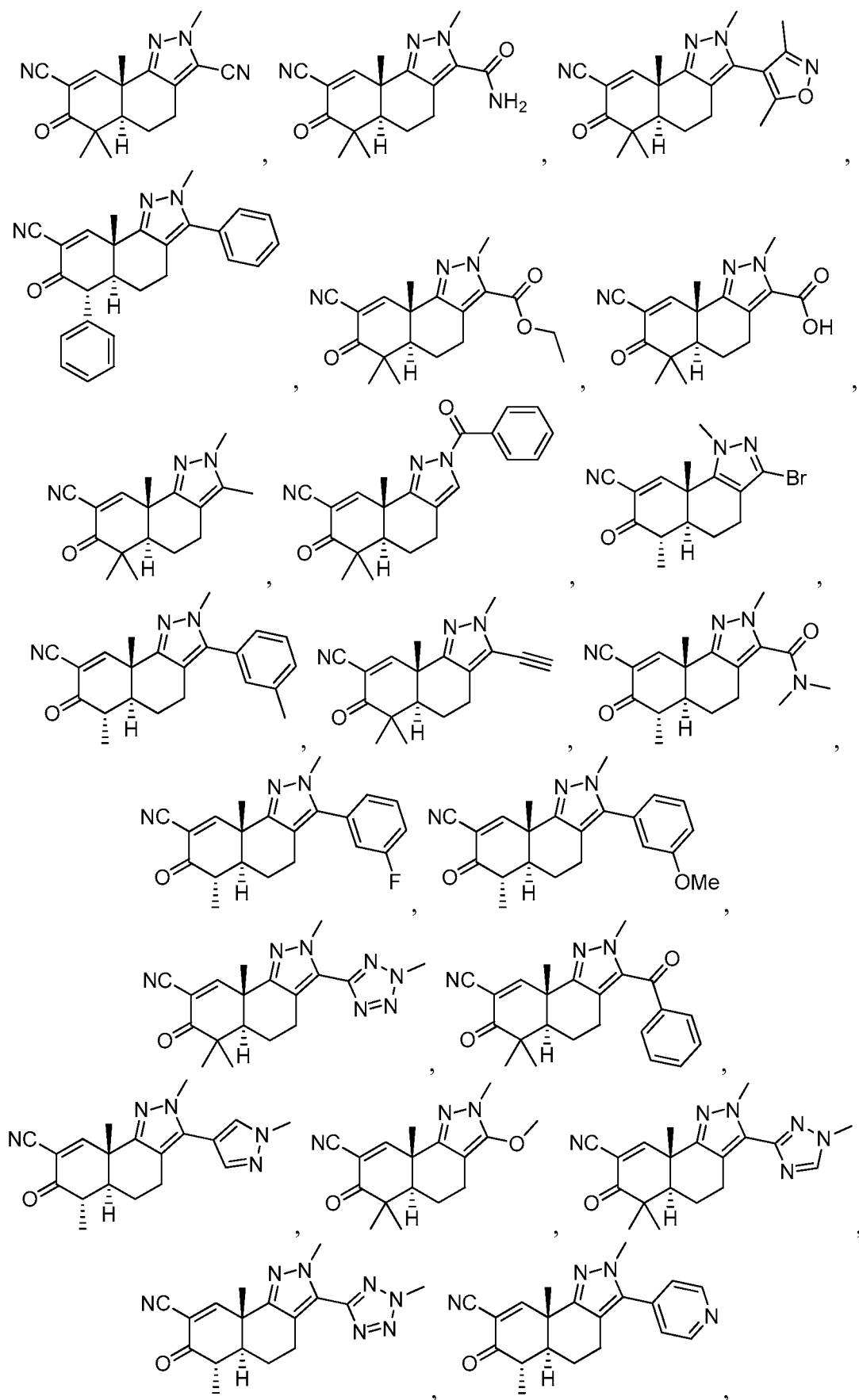




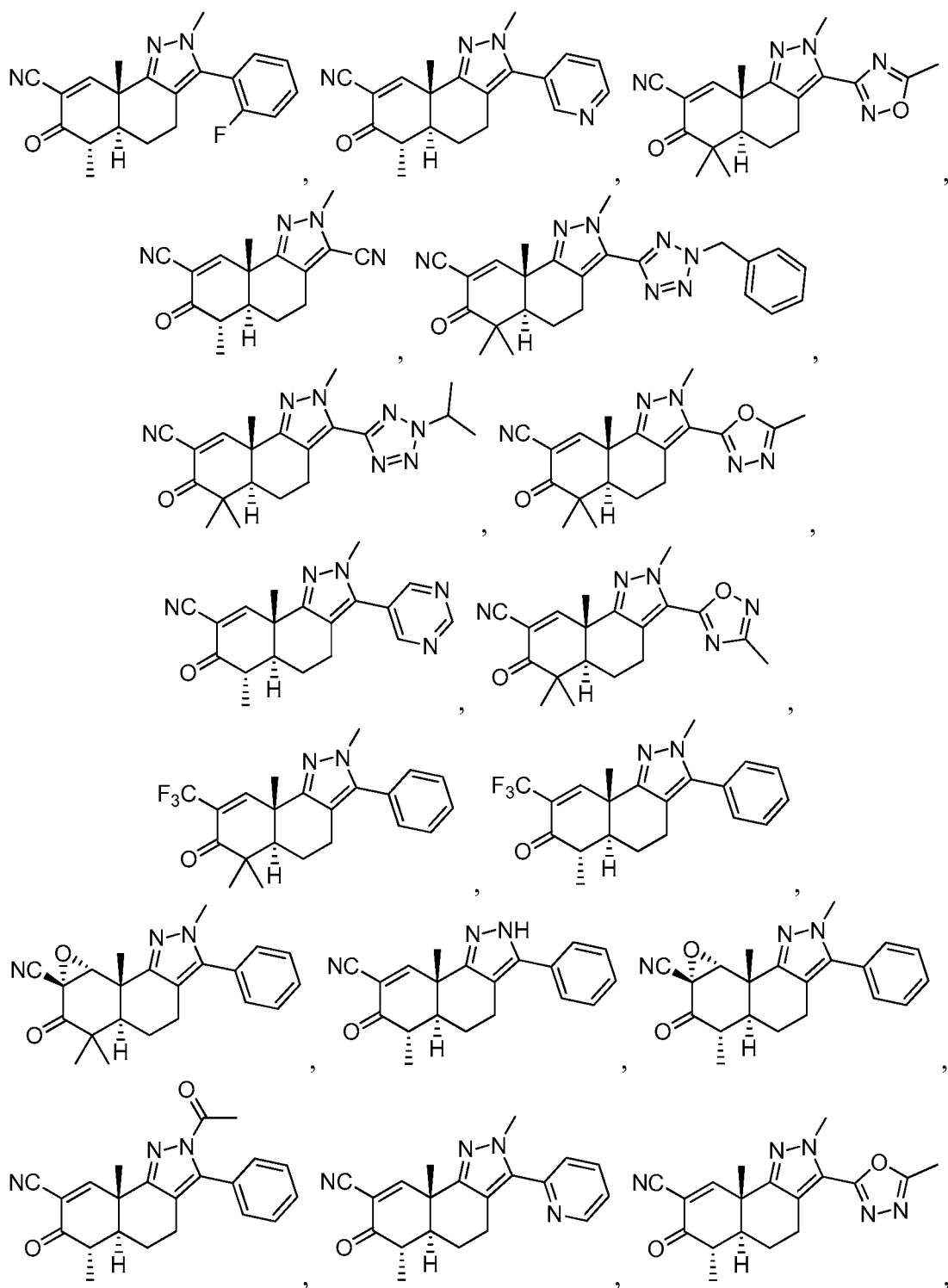


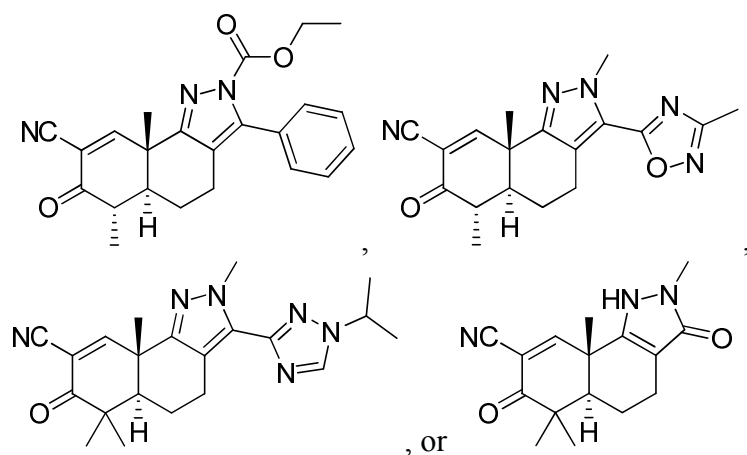
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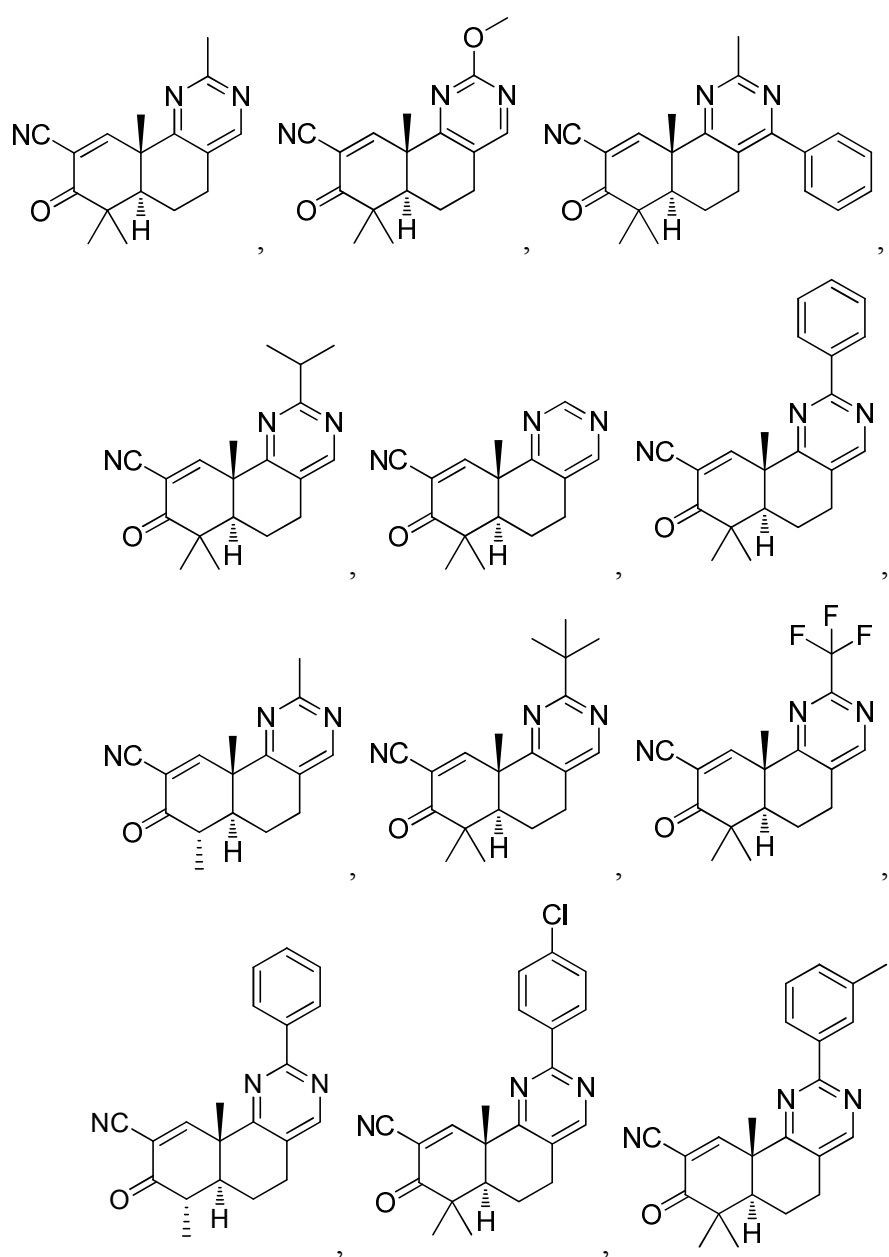


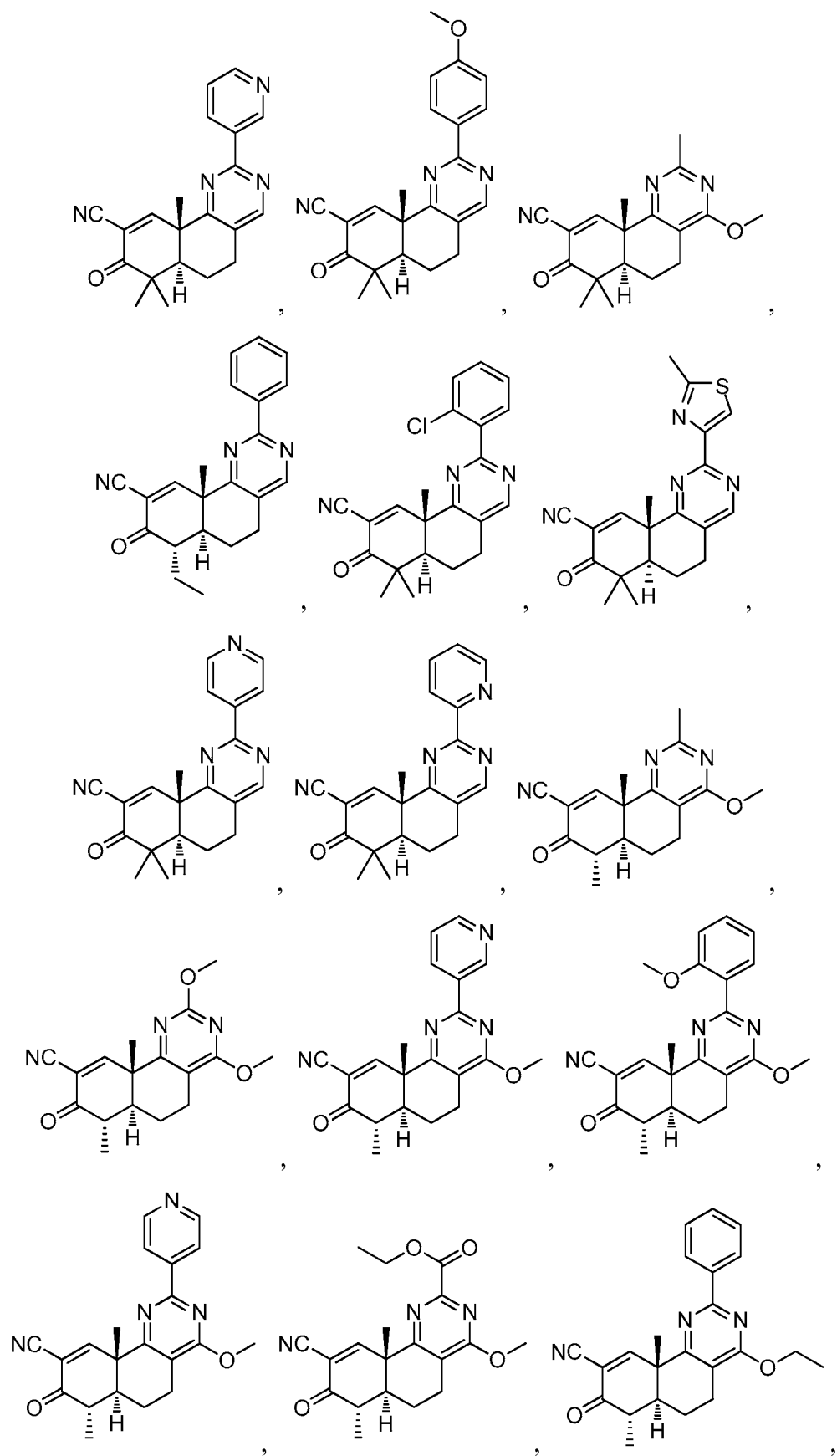
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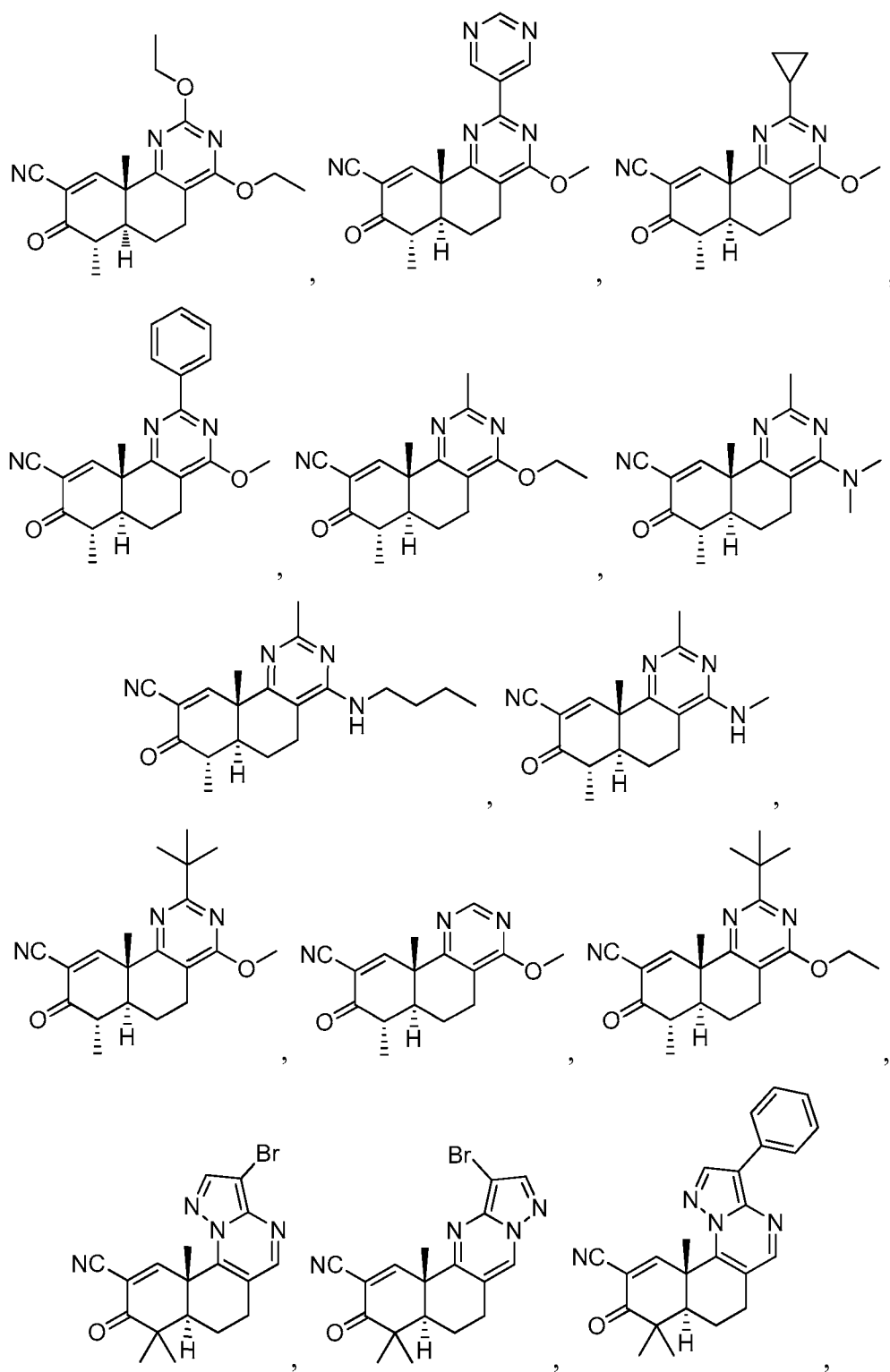


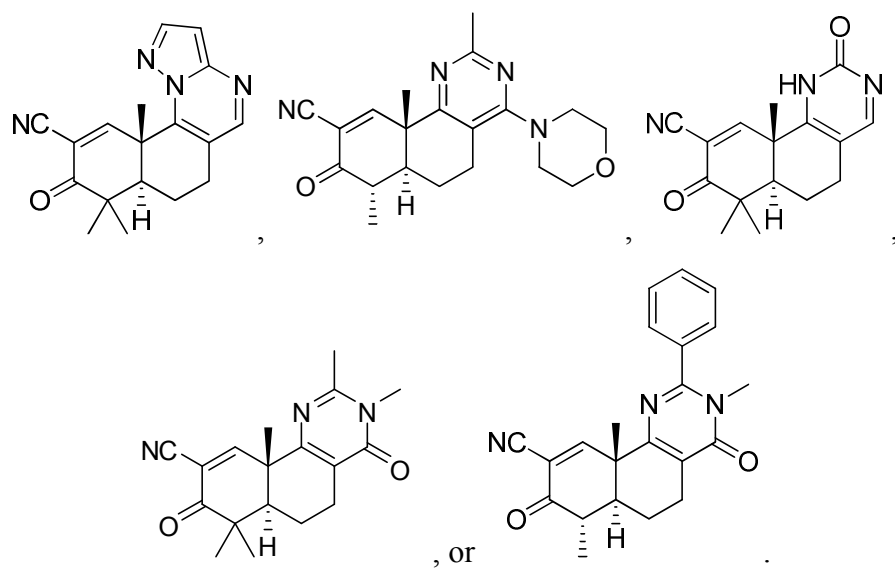


In some examples, the compounds are further defined as:

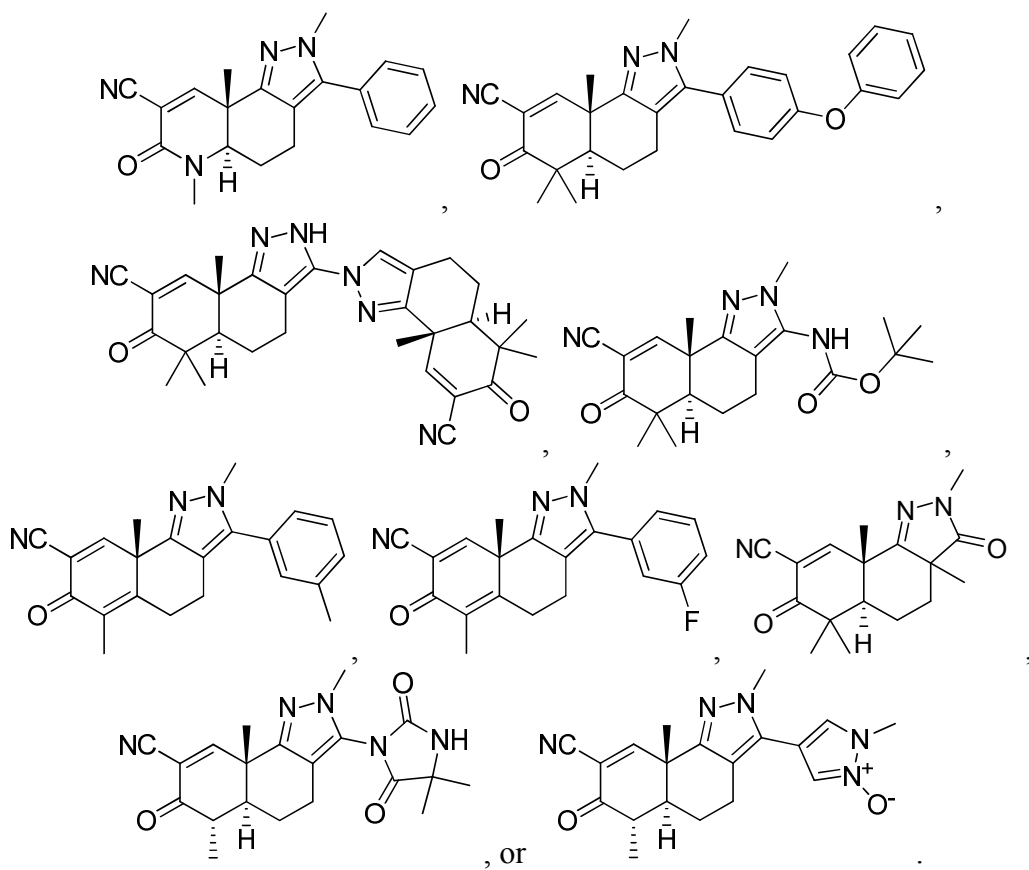




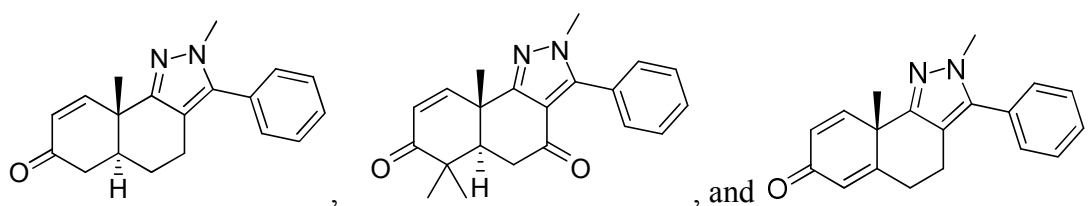




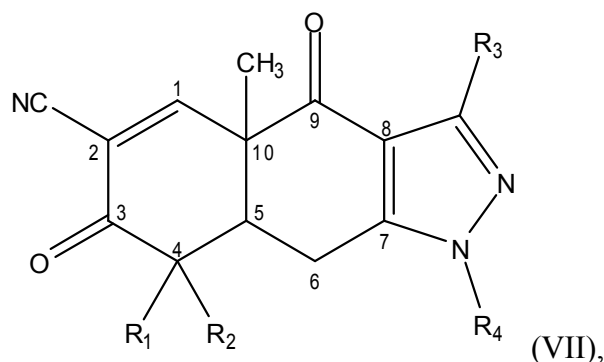
In another example, the disclosure describes compounds of the formulas:



In another example, the disclosure describes compounds of the formulas:



In another example, the disclosure describes compounds of the formula:



wherein:

R₁ and R₂ are each independently:

- 5 hydrogen, hydroxy or amino; or
- alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), hetero-
- aryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryl-
- oxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12),
- 10 alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkyl-
- amino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted
- version of any of these groups; or

- R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12),
- arenediyl_(C≤12), alkoxydiyl_(C≤12), alkenyloxydiyl_(C≤12), alkyl-
- aminodiyl_(C≤12), alkenylaminodiyl_(C≤12), or a substituted version
- 15 of any of these groups;

R₃ is:

- hydrogen, hydroxy or amino, or
- alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), hetero-
- aryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryl-
- 20 oxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12),
- alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkyl-
- amino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted
- version of any of these groups; and

R₄ is:

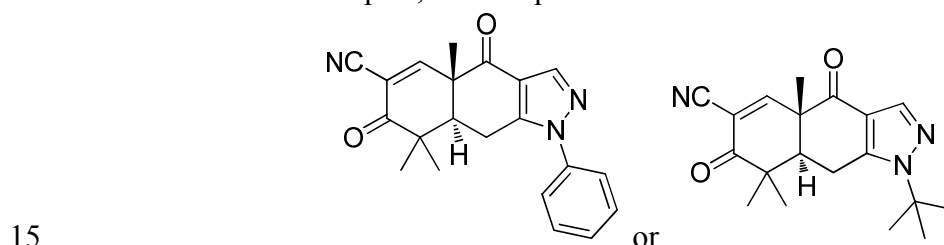
- 25 hydrogen; or

alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), hetero-aryl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups;

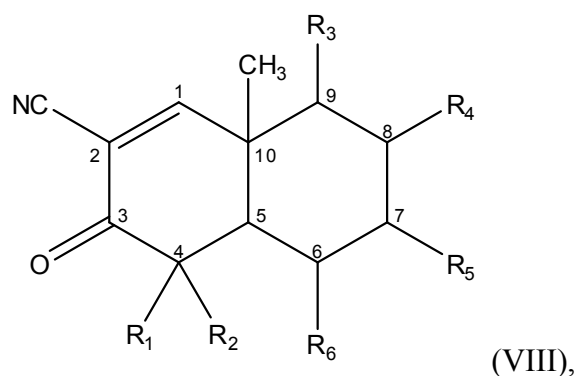
or a pharmaceutically acceptable salt or tautomer thereof.

- 5 In some examples, R₁ or R₂ is alkyl_(C≤8) or substituted alkyl_(C≤8). In some examples, R₁ and R₂ are alkyl_(C≤8). In some examples, R₁ and R₂ are methyl. In some examples, R₃ is hydrogen. In some examples, R₄ is aryl_(C≤8) or substituted aryl_(C≤8). In some examples, R₄ is aryl_(C≤8). In some examples, R₄ is phenyl. In some examples, R₄ is alkyl_(C≤6) or substituted alkyl_(C≤6). In some examples, R₄ is alkyl_(C≤6). In some examples, R₄ is *t*-butyl. In some examples, carbon atom 10 is in the *R* configuration. In some examples, carbon atom 10 is in the *S* configuration. In some examples, carbon atom 5 is in the *R* configuration. In some examples, carbon atom 5 is in the *S* configuration.

In some examples, the compounds are further defined as:



In another example, the disclosure describes compounds of the formula:



wherein:

- 20 R₁ and R₂ are each independently:
hydrogen, hydroxy or amino; or
alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), hetero-aryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), aryl-oxy_(C≤12), aralkoxy_(C≤12), heteroaryloxy_(C≤12), acyloxy_(C≤12),

alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups; or

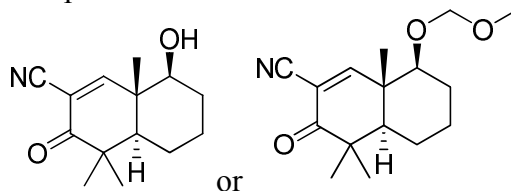
5 R₁ and R₂ are taken together and are alkanediyl_(C≤12), alkenediyl_(C≤12), arenediyl_(C≤12), alkoxydiyl_(C≤12), alkenyloxydiyl_(C≤12), alkylaminodiyl_(C≤12), alkenylaminodiyl_(C≤12), or a substituted version of any of these groups; and

R₃, R₄, R₅ and R₆ are each independently:

hydrogen, hydroxy or amino, or
10 alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), arylalkoxy_(C≤12), heteroarylalkoxy_(C≤12), acyloxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), arylamino_(C≤12), aralkylamino_(C≤12), heteroarylamino_(C≤12), amido_(C≤12), or a substituted version of any of
15 these groups; and

or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, R₁ or R₂ is alkyl_(C≤8) or substituted alkyl_(C≤8). In some examples, R₁ and R₂ are alkyl_(C≤8). In some examples, R₁ and R₂ are methyl. In some examples, R₄, R₅ and R₆ are hydrogen. In some examples, R₃ is hydroxy. In some
20 examples, R₄ is alkoxy_(C≤6) or substituted alkoxy_(C≤6). In some examples, R₄ is substituted alkoxy_(C≤6). In some examples, R₄ is methoxymethoxy. In some examples, carbon atom 10 is in the *R* configuration. In some examples, carbon atom 10 is in the *S* configuration. In some examples, carbon atom 5 is in the *R* configuration. In some examples, carbon atom 5 is in the *S* configuration.
25 In some examples, the compounds are further defined as:



In another example, the disclosure describes pharmaceutical compositions comprising the compound according to any of the formulas disclosed herein and an

excipient. In some examples, the pharmaceutical compositions are further defined as:

- a) the compound according to any of the formulas disclosed herein;
- b) an optical isomer of the compound, wherein the optical isomer is the enantiomer of the compound; and
- 5 c) an excipient.

In some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 1:1. In some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 5:1. In some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 10:1. In
10 some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 20:1.

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
15 embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula doesn't mean that it cannot also belong to another generic formula.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

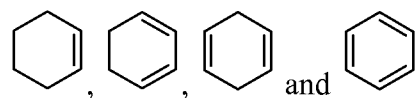
Disclosed herein are new compounds and compositions with antioxidant and/or anti-inflammatory properties, methods for their manufacture, and methods for their use, including for the treatment and/or prevention of disease.

5 I. Definitions

When used in the context of a chemical group, “hydrogen” means $-H$; “hydroxy” means $-OH$; “oxo” means $=O$; “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”
 10 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 $-SH$; “thio” means $=S$; “sulfonyl” means $-S(O)_2-$; and “sulfinyl” means $-S(O)-$.

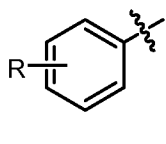
In the context of chemical formulas, the symbol “ $-$ ” means a single bond, “ $=$ ”
 15 means a double bond; and “ $\equiv$ ” means triple bond. An “epoxidized double bond” represents the group: . The symbol “ $----$ ” represents an optional bond, which if present is either single or double. The symbol “ $=====$ ” represents a single bond or a

double bond. Thus, for example, the structure  includes the structures ,

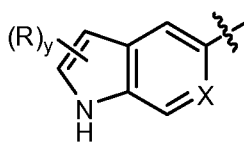


and . As will be understood by a person of skill in the art,
 20 no one such ring atom forms part of more than one double bond. The symbol “”, when drawn perpendicularly across a bond indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups in order to assist the reader in rapidly and unambiguously identifying a point of attachment. The symbol “” means a single bond where the
 25 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 conformation (*e.g.*, either *R* or *S*) or the geometry is undefined (*e.g.*, either *E* or *Z*).

Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to the atom. When a group “R” is depicted as a “floating group” on a ring system, for example, in the formula:



- 5 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:



- 10 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
 15 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,
 20 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.

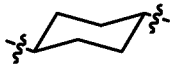
- For the groups and classes below, the following parenthetical subscripts further define the group/class as follows: “(C_n)” defines the exact number (n) of carbon atoms in the group/class. “(C_{≤n})” defines the maximum number (n) of carbon atoms that can be in the group/class, with the minimum number as small as possible
 25 for the group in question, *e.g.*, it is understood that the minimum number of carbon atoms in the group “alkenyl_(C_{≤8})” or the class “alkene_(C_{≤8})” is two. For example, “alkoxy_(C_{≤10})” designates those alkoxy groups having from 1 to 10 carbon atoms (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (*e.g.*, 3 to 10 carbon

atoms). (C_n-n') defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Similarly, "alkyl_(C2-10)" designates those alkyl groups having from 2 to 10 carbon atoms (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (*e.g.*, 3 to 10 carbon atoms)).

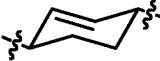
5 The term "saturated" as used herein means the compound or group so modified has no carbon-carbon double and no carbon-carbon triple bonds, except as noted below. The term does not preclude carbon-heteroatom multiple bonds, for example a carbon oxygen double bond or a carbon nitrogen double bond. Moreover, it does not preclude a carbon-carbon double bond that may occur as part of keto-enol
10 tautomerism or imine/enamine tautomerism.

 The term "aliphatic" when used without the "substituted" modifier signifies that the compound/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
15 (alicyclic). Aliphatic compounds/groups can be saturated, that is joined by single bonds (alkanes/alkyl), or unsaturated, with one or more double bonds (alkenes/alkenyl) or with one or more triple bonds (alkynes/alkynyl). When the term "aliphatic" is used without the "substituted" modifier only carbon and hydrogen atoms are present. When the term is used with the "substituted" modifier one or more
20 hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.

 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
25 linear or branched, cyclo, cyclic or acyclic structure, and no atoms other than carbon and hydrogen. Thus, as used herein cycloalkyl is a subset of alkyl. The groups -CH₃ (Me), -CH₂CH₃ (Et), -CH₂CH₂CH₃ (*n*-Pr), -CH(CH₃)₂ (*iso*-Pr), -CH(CH₂)₂ (cyclopropyl), -CH₂CH₂CH₂CH₃ (*n*-Bu), -CH(CH₃)CH₂CH₃ (*sec*-butyl), -CH₂CH(CH₃)₂ (*iso*-butyl), -C(CH₃)₃ (*tert*-butyl), -CH₂C(CH₃)₃ (*neo*-pentyl),
30 cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexylmethyl 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, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and

hydrogen. The groups, $-\text{CH}_2-$ (methylene), $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, and , are non-limiting examples of alkanediyl groups. The term “alkylidene” when used without the “substituted” modifier refers to the divalent group $=\text{CRR}'$ in which R and R' are independently hydrogen, alkyl, or R and R' are taken together to represent an alkanediyl having at least two carbon atoms. Non-limiting examples of alkylidene groups include: $=\text{CH}_2$, $=\text{CH}(\text{CH}_2\text{CH}_3)$, and $=\text{C}(\text{CH}_3)_2$. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The following groups are non-limiting examples of substituted alkyl groups: $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{CH}_2\text{Cl}$. The term “haloalkyl” is a subset of substituted alkyl, in which one or more hydrogen has been substituted with a halo group and no other atoms aside from carbon, hydrogen and halogen are present. The group, $-\text{CH}_2\text{Cl}$ is a non-limiting examples of a haloalkyl. An “alkane” refers to the compound $\text{H}-\text{R}$, wherein R is alkyl. The term “fluoroalkyl” is a subset of substituted alkyl, in which one or more hydrogen has been substituted with a fluoro group and no other atoms aside from carbon, hydrogen and fluorine are present. The groups, $-\text{CH}_2\text{F}$, $-\text{CF}_3$, and $-\text{CH}_2\text{CF}_3$ are non-limiting examples of fluoroalkyl groups. An “alkane” refers to the compound $\text{H}-\text{R}$, wherein R is alkyl.

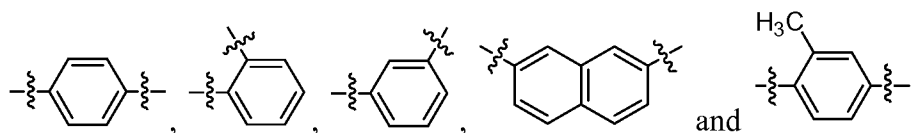
The term “alkenyl” when used without the “substituted” modifier refers to an monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: $-\text{CH}=\text{CH}_2$ (vinyl), $-\text{CH}=\text{CHCH}_3$, $-\text{CH}=\text{CHCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}=\text{CH}_2$ (allyl), $-\text{CH}_2\text{CH}=\text{CHCH}_3$, and $-\text{CH}=\text{CH}-\text{C}_6\text{H}_5$. 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, cyclo, cyclic or 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, $-\text{CH}=\text{CH}-$,

$-\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}=\text{CHCH}_2-$, and , are non-limiting examples of alkenediyl groups. When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$,
 5 $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups, $-\text{CH}=\text{CHF}$, $-\text{CH}=\text{CHCl}$ and $-\text{CH}=\text{CHBr}$, are non-limiting examples of substituted alkenyl groups. An “alkene” refers to the compound $\text{H}-\text{R}$, wherein R is alkenyl.

The term “alkynyl” 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, cyclo, cyclic or acyclic structure, at least one
 10 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, $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, and $-\text{CH}_2\text{C}\equiv\text{CCH}_3$, are non-limiting examples of alkynyl groups. When alkynyl is used with the
 15 “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. An “alkyne” refers to the compound $\text{H}-\text{R}$, wherein R is alkynyl.

The term “heteroaryl” when used without the “substituted” modifier refers to a
 20 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. As used herein,
 25 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. If more than one ring is present, the rings may be fused or unfused. Non-limiting examples of heteroaryl groups include furanyl, imidazolyl, indolyl, indazolyl (Im), isoxazolyl, methylpyridinyl, phenylpyridinyl, oxazolyl,
 30 pyrazolyl, pyridinyl, pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, triazinyl, tetrazolyl, thienyl, and triazolyl. The term “heteroarenediyl” when used without the “substituted” modifier refers to an divalent aromatic group, with two aromatic carbon atoms, two aromatic nitrogen atoms, or one aromatic carbon

atom and one aromatic nitrogen atom as the two points of attachment, said atoms forming part of one or more aromatic ring structure(s) wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. 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. If more than one ring is present, the rings may be fused or unfused. Non-limiting examples of heteroarenediyl groups include:

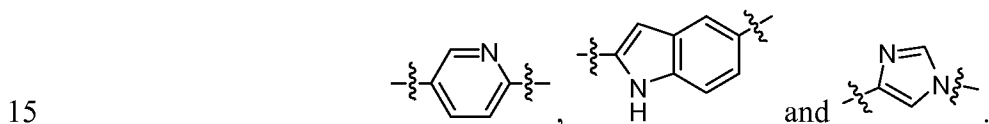


When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. An “arene” refers to the compound $\text{H}-\text{R}$, wherein R is aryl.

The term “aralkyl” when used without the “substituted” modifier refers to the monovalent group $-\text{alkanediyl-aryl}$, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: phenylmethyl (benzyl, Bn) and 2-phenyl-ethyl. When the term is used with the “substituted” modifier one or more hydrogen atom from the alkanediyl and/or the aryl has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. 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. 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. If more than one ring is present, the rings may be fused or

unfused. Non-limiting examples of heteroaryl groups include furanyl, imidazolyl, indolyl, indazolyl (Im), isoxazolyl, methylpyridinyl, oxazolyl, phenylpyridinyl, pyridinyl, pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, triazinyl, tetrazolyl, thiazolyl, thienyl, and triazolyl. The term “heteroarenediyl” when
 5 used without the “substituted” modifier refers to an divalent aromatic group, with two aromatic carbon atoms, two aromatic nitrogen atoms, or one aromatic carbon atom and one aromatic nitrogen atom as the two points of attachment, said atoms forming part of one or more aromatic ring structure(s) wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the divalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen, aromatic oxygen and aromatic sulfur. As
 10 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. If more than one ring is present, the rings may be fused or unfused. Non-limiting examples of heteroarenediyl groups include:



When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.

20 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
 25 carbon, hydrogen, nitrogen, oxygen and sulfur. 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. If more than one ring is present, the rings may be fused or unfused. Non-limiting examples of heterocycloalkyl groups include aziridinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, and
 30 pyranlyl. When the term “heterocycloalkyl” used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$,

$-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “acyl” when used without the “substituted” modifier refers to the group $-\text{C}(\text{O})\text{R}$, in which R is a hydrogen, alkyl, aryl, aralkyl or heteroaryl, as those terms are defined above. The groups, $-\text{CHO}$, $-\text{C}(\text{O})\text{CH}_3$ (acetyl, Ac), $-\text{C}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{CH}(\text{CH}_2)_2$, $-\text{C}(\text{O})\text{C}_6\text{H}_5$, $-\text{C}(\text{O})\text{C}_6\text{H}_4\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{C}_6\text{H}_5$, $-\text{C}(\text{O})$ (imidazolyl) are non-limiting examples of acyl groups. A “thioacyl” is defined in an analogous manner, except that the oxygen atom of the group $-\text{C}(\text{O})\text{R}$ has been replaced with a sulfur atom, $-\text{C}(\text{S})\text{R}$. When either of these terms are used with the “substituted” modifier one or more hydrogen atom (including the hydrogen atom directly attached the carbonyl or thiocarbonyl group) has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups, $-\text{C}(\text{O})\text{CH}_2\text{CF}_3$, $-\text{CO}_2\text{H}$ (carboxyl), $-\text{CO}_2\text{CH}_3$ (methylcarboxyl), $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NH}_2$ (carbamoyl), and $-\text{CON}(\text{CH}_3)_2$, are non-limiting examples of substituted acyl groups.

The term “alkoxy” when used without the “substituted” modifier refers to the group $-\text{OR}$, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkoxy groups include: $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OCH}(\text{CH}_2)_2$, $-\text{O}$ -cyclopentyl, and $-\text{O}$ -cyclohexyl. The terms “alkenyloxy”, “alkynyloxy”, “aryloxy”, “aralkoxy”, “heteroaryloxy”, and “acyloxy”, when used without the “substituted” modifier, refers to groups, defined as $-\text{OR}$, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, and acyl, respectively. The term “alkoxydiyl” refers to the divalent group $-\text{O}$ -alkanediyl-, $-\text{O}$ -alkanediyl- O -, or $-\text{O}$ -alkanediyl- O -alkanediyl-. The term “alkylthio” when used without the “substituted” modifier refers to the group $-\text{SR}$, 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 has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$. 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 “alkylamino” when used without the “substituted” modifier refers to the group $-\text{NHR}$, in which R is an alkyl, as that term is defined above. Non-limiting

examples of alkylamino groups include: -NHCH_3 and $\text{-NHCH}_2\text{CH}_3$. The term “dialkylamino” when used without the “substituted” modifier refers to the group $\text{-NRR}'$, 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: $\text{-N(CH}_3)_2$, $\text{-N(CH}_3)(\text{CH}_2\text{CH}_3)$, and *N*-pyrrolidinyl. The terms “alkoxyamino”, “alkenylamino”, “alkynylamino”, “arylamino”, “aralkylamino”, “heteroarylamino”, and “alkylsulfonylamino” when used without the “substituted” modifier, refers to groups, defined as -NHR , in which R is alkoxy, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, and alkylsulfonyl, respectively. A non-limiting example of an arylamino group is $\text{-NHC}_6\text{H}_5$. 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. The term “alkylaminodiyl” refers to the divalent group -NH-alkanediyl- , $\text{-NH-alkanediyl-NH-}$, or $\text{-alkanediyl-NH-alkanediyl-}$. 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 , $\text{-CO}_2\text{H}$, $\text{-CO}_2\text{CH}_3$, -CN , -SH , -OCH_3 , $\text{-OCH}_2\text{CH}_3$, -C(O)CH_3 , $\text{-N(CH}_3)_2$, -C(O)NH_2 , -OC(O)CH_3 , or $\text{-S(O)}_2\text{NH}_2$. The groups -NHC(O)OCH_3 and -NHC(O)NHCH_3 are non-limiting examples of substituted amido groups.

The terms “alkylsulfonyl” and “alkylsulfinyl” when used without the “substituted” modifier refers to the groups $\text{-S(O)}_2\text{R}$ and -S(O)R , respectively, in which R is an alkyl, as that term is defined above. The terms “alkenylsulfonyl”, “alkynylsulfonyl”, “arylsulfonyl”, “aralkylsulfonyl”, and “heteroarylsulfonyl”, are defined in an analogous manner. 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 , $\text{-CO}_2\text{H}$, $\text{-CO}_2\text{CH}_3$, -CN , -SH , -OCH_3 , $\text{-OCH}_2\text{CH}_3$, -C(O)CH_3 , $\text{-N(CH}_3)_2$, -C(O)NH_2 , -OC(O)CH_3 , or $\text{-S(O)}_2\text{NH}_2$.

As used herein, a “chiral auxiliary” refers to a removable chiral group that is capable of influencing the stereoselectivity of a reaction. Persons of skill in the art are familiar with such compounds, and many are commercially available.

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
5 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
10 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.

The term “hydrate” when used as a modifier to a compound means that the
15 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 “IC₅₀” refers to an inhibitory dose which is 50% of the maximum response obtained. This quantitative measure indicates how much of a
20 particular drug or other substance (inhibitor) is needed to inhibit a given biological, biochemical or chemical process (or component of a process, *i.e.* an enzyme, cell, cell receptor or microorganism) by half.

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

As used herein, the term “patient” or “subject” refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and
30 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
5 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),
10 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,
15 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 alkanolic acids, propionic acid, *p*-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid,
20 trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine,
25 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
30 Acta, 2002).

“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.

5 “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*
10 *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, quinate, esters of amino acids, and the like. Similarly, a
15 compound comprising an amine group may be administered as an amide that is converted by hydrolysis *in vivo* to the amine compound.

The term “saturated” when referring to an atom means that the atom is connected to other atoms only by means of single bonds.

A “stereoisomer” or “optical isomer” is an isomer of a given compound in
20 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
25 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
30 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 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).

“Effective amount,” “Therapeutically effective amount” or “pharmaceutically effective amount” means that amount which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

“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.

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; IFN γ or IFN- γ , interferon- γ ; TNF α or TNF- α , tumor necrosis factor- α ; IL-1 β , interleukin-1 β ; HO-1, inducible heme oxygenase.

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

II. Compounds and Synthetic Methods

The compounds provided by the present disclosure are shown above in the summary of the invention section and in the claims below. They may be made using the 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* (2007), which is incorporated by reference herein.

Compounds employed in methods 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 structure 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, as defined by the IUPAC 1974 Recommendations. For example, mixtures of stereoisomers may be separated using the techniques taught in the Examples section below, as well as modifications thereof.

Atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Compounds of the present invention include those with one or more atoms that have been isotopically modified or enriched, in particular those with pharmaceutically acceptable isotopes or those useful for pharmaceutically research. 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 deuterium and tritium, and isotopes of carbon include ^{13}C and ^{14}C . Similarly, it is contemplated that one or more carbon atom(s) of a compound of the present invention may be replaced by a silicon atom(s). Furthermore, it is contemplated that one or more oxygen atom(s) of a compound of the present invention may be replaced by a sulfur or selenium atom(s).

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 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* (2002), which is incorporated herein by reference.

It should be further recognized that the compounds of the present invention include those that have been further modified to comprise substituents that are convertible to hydrogen *in vivo*. This includes those groups that may be convertible to a hydrogen atom by enzymological or chemical means including, but not limited to, hydrolysis and hydrogenolysis. Examples include hydrolyzable groups, such as acyl groups, groups having an oxycarbonyl group, amino acid residues, peptide residues, *o*-nitrophenylsulfenyl, trimethylsilyl, tetrahydropyranyl, diphenylphosphinyl, and the like. Examples of acyl groups include formyl, acetyl, trifluoroacetyl, and the like. Examples of groups having an oxycarbonyl group include ethoxycarbonyl, *tert*-butoxycarbonyl ($-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$), benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, vinyloxycarbonyl, β -(*p*-toluenesulfonyl)ethoxycarbonyl, and the like. Suitable amino acid residues include, but are not limited to, residues of Gly (glycine), Ala (alanine), Arg (arginine), Asn (asparagine), Asp (aspartic acid), Cys (cysteine), Glu (glutamic acid), His (histidine), Ile (isoleucine), Leu (leucine), Lys (lysine), Met (methionine), Phe (phenylalanine), Pro (proline), Ser (serine), Thr (threonine), Trp (tryptophan), Tyr (tyrosine), Val (valine), Nva (norvaline), Hse (homoserine), 4-Hyp (4-hydroxyproline), 5-Hyl (5-hydroxylysine), Orn (ornithine) and β -Ala. Examples of suitable amino acid residues also include amino acid residues that are protected with a protecting group. Examples of suitable protecting groups

include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethoxycarbonyl groups (such as benzyloxycarbonyl and *p*-nitrobenzyloxycarbonyl), *tert*-butoxycarbonyl groups ($-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$), and the like. Suitable peptide residues include peptide residues comprising two to five amino acid residues. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric carbon atom include residues of Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr and Tyr. Peptide residues having an asymmetric carbon atom include peptide residues having one or more constituent amino acid residues having an asymmetric carbon atom. Examples of suitable amino acid protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethoxycarbonyl groups (such as benzyloxycarbonyl and *p*-nitrobenzyloxycarbonyl), *tert*-butoxycarbonyl groups ($-\text{C}(\text{O})\text{OC}(\text{CH}_3)_3$), and the like. Other examples of substituents “convertible to hydrogen *in vivo*” include reductively eliminable hydrogenolyzable groups. Examples of suitable reductively eliminable hydrogenolyzable groups include, but are not limited to, arylsulfonyl groups (such as *o*-toluenesulfonyl); methyl groups substituted with phenyl or benzyloxy (such as benzyl, trityl and benzyloxymethyl); arylmethoxycarbonyl groups (such as benzyloxycarbonyl and *o*-methoxy-benzyloxycarbonyl); and haloethoxycarbonyl groups (such as β,β,β -trichloroethoxycarbonyl and β -iodoethoxycarbonyl).

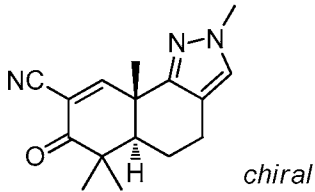
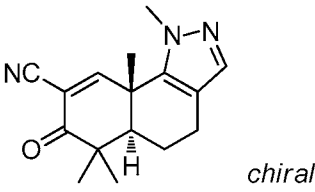
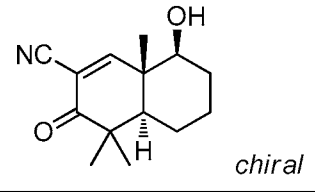
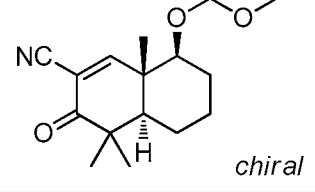
Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (*e.g.*, higher oral bioavailability 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.

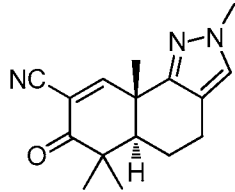
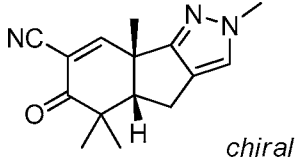
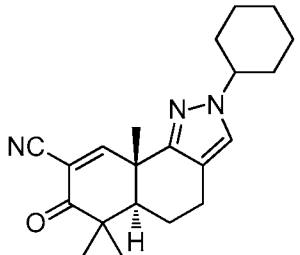
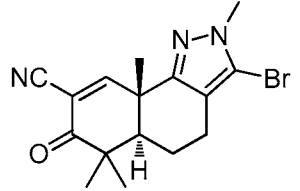
III. Biological Activity

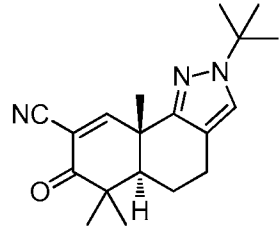
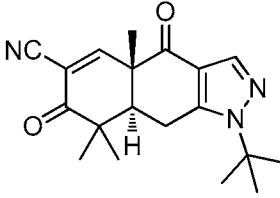
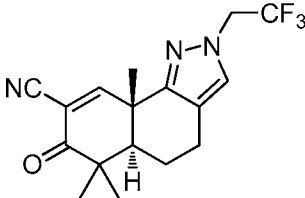
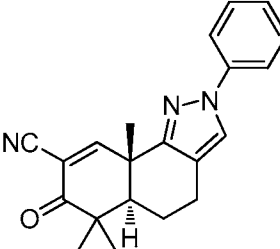
Assay results for the suppression of IFN γ -induced NO production are shown for several of the compounds of the present invention in Table 1 below. In the right-hand column of this table under the RAW264.7 heading, the results are compared to

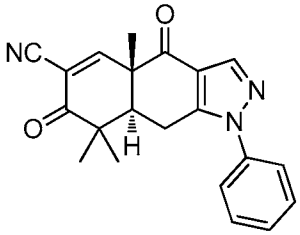
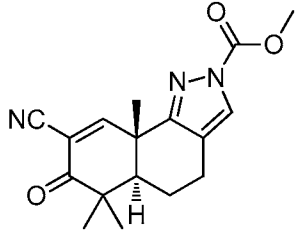
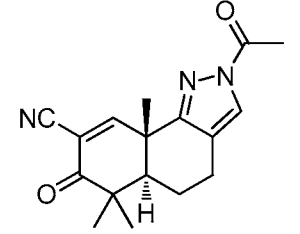
those of bardoxolone methyl (RTA 402). NQO1-ARE Luciferase Reporter Assay results are shown in the last column. Details regarding both assays are provided in the Examples section below. Except for those formulas labeled “chiral,” each compound depicted in Table 1 is racemic. For the racemic compounds, the molecular structure
5 shown is the formula of one of the two enantiomers. For those formulas labeled “chiral,” the molecular formula shows the predominant stereoisomer present.

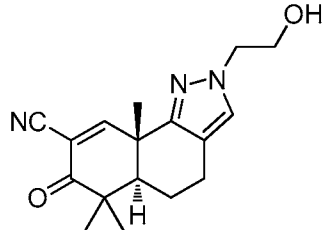
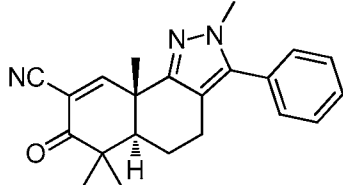
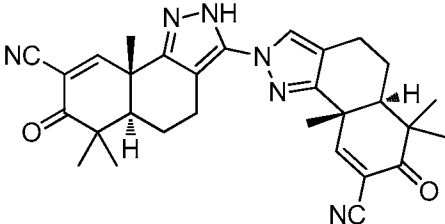
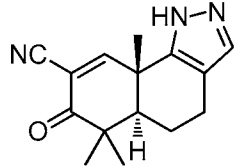
Table 1. Suppression of IFN γ -Induced NO Production.

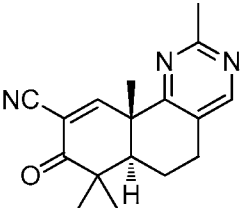
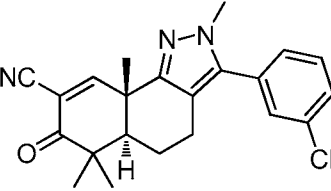
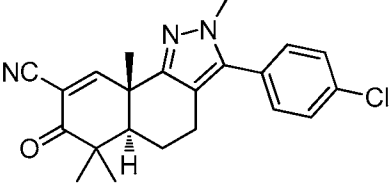
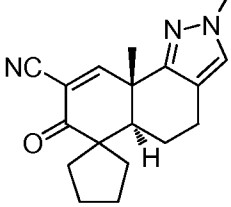
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63341		269.34	70	--	1.7
TX63342		269.34	180	40	
TX63363		233.31	>200	--	
TX63364		277.36	>200	--	

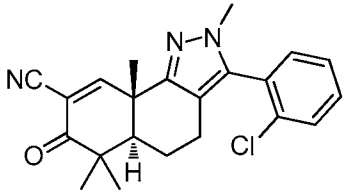
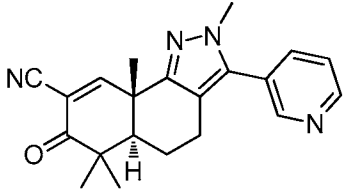
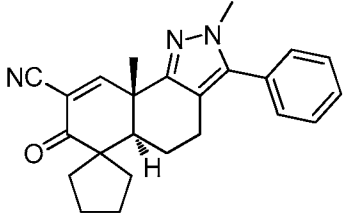
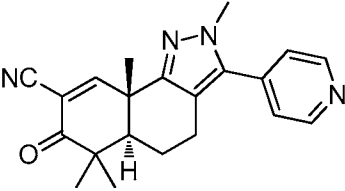
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63432		269.34	166	68	
TX63436	 <i>chiral</i>	255.31	>200	--	
TX63444		337.46	140	108	
TX63445		348.24	37.9	23	

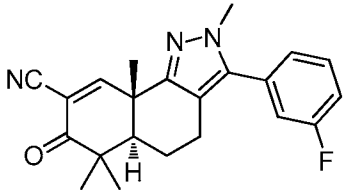
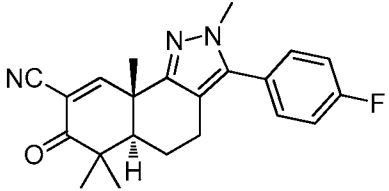
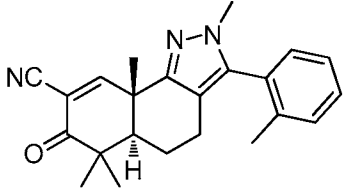
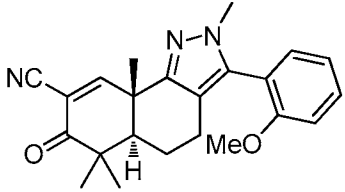
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63450		311.42	148	49	
TX63451		325.40	137	45	
TX63454		337.30	134	44	
TX63455		331.40	109	62	

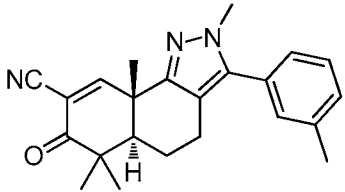
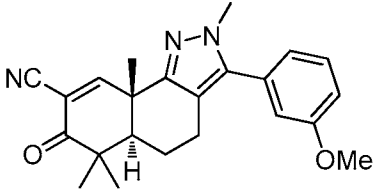
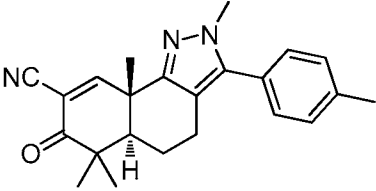
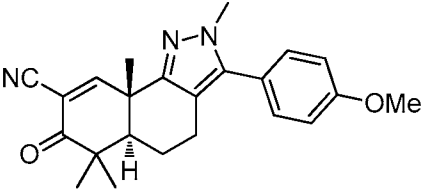
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63456		345.40	>200	--	
TX63462		313.35	147	77	
TX63463		297.35	205	108	

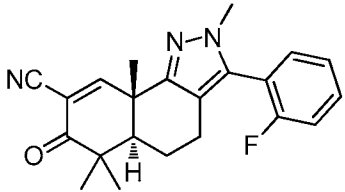
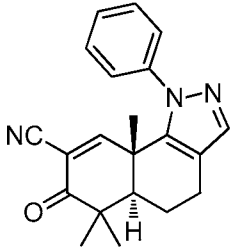
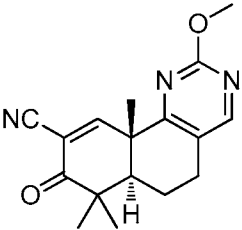
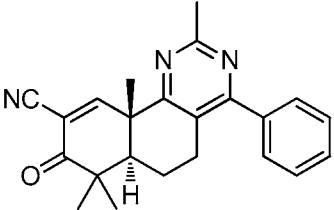
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63464		299.37	>200	--	
TX63465		345.44	18.3	11	4.8
TX63466		508.61	10.4	4.5	
TX63467		255.31	>200	--	

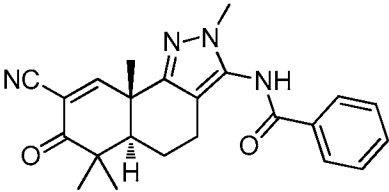
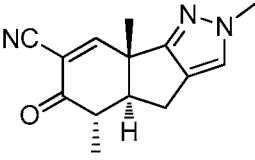
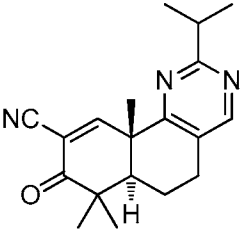
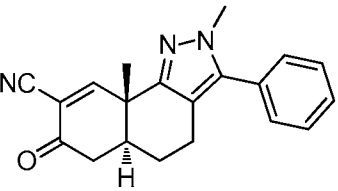
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63468		281.35	64	33.7	2.0
TX63485		379.88	34	24.3	
TX63486		379.88	48	34.3	
TX63487		295.38	85	60.7	

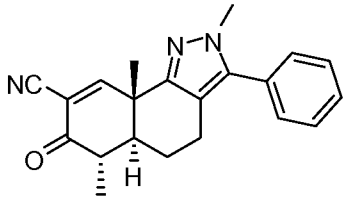
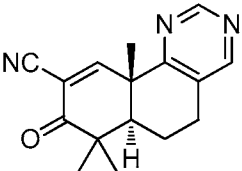
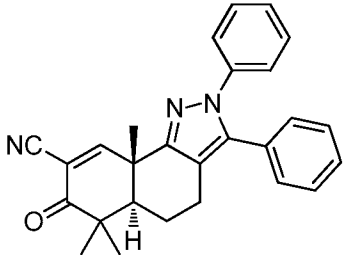
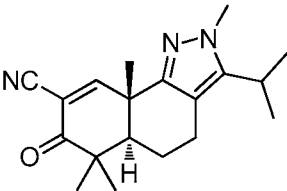
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63491		379.90	35	15.2	
TX63503		346.43	17	7.4	5.5
TX63504		371.47	20	8.9	
TX63505		346.43	16	6.9	6.8

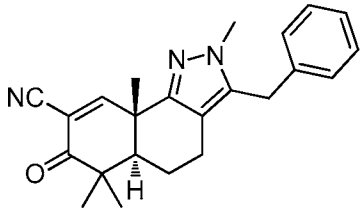
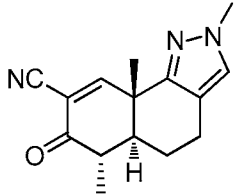
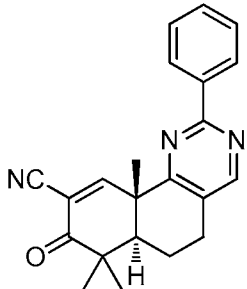
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63506		363.43	25	15.6	3.2
TX63507		363.43	39	24.4	
TX63508		359.48	33	20.6	
TX63509		375.47	38	23.8	

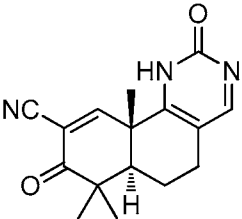
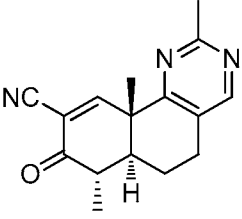
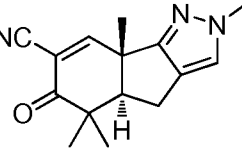
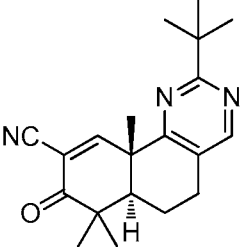
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63512		359.47	25	20.8	1.4
TX63513		375.47	25	20.8	2.9
TX63514		359.47	37	30.8	
TX63515		375.47	35	29.2	

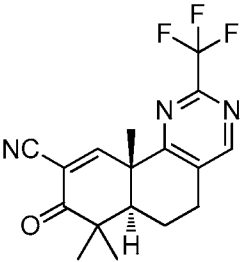
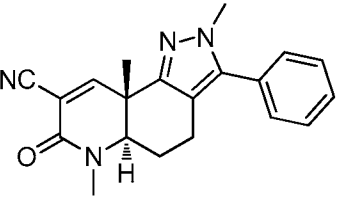
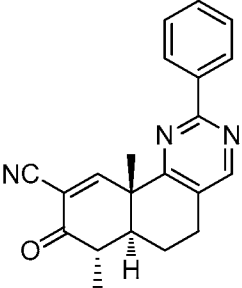
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63519		363.43	21	14	2.5
TX63524		331.41	68	48.6	
TX63528		297.36	85	56.7	
TX63529		357.45	46	30.7	

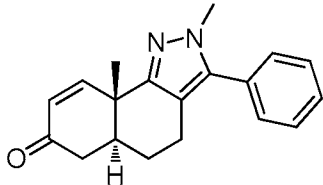
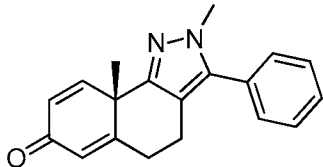
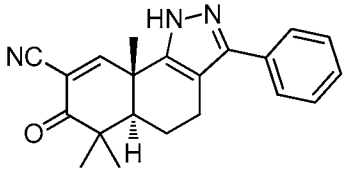
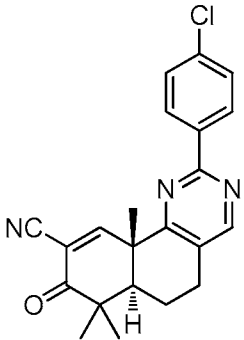
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63531		388.47	>200	--	1.1
TX63533		241.29	>200	--	
TX63534		309.41	49	23.3	
TX63540		317.39	66.8	45.0	1.6

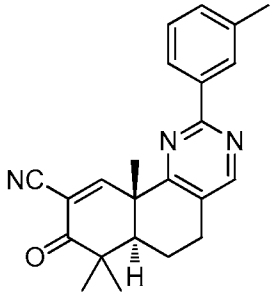
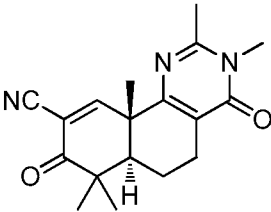
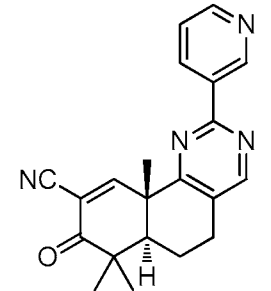
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63541		331.41	6	3.7	4.4
TX63542		267.33	55	36.7	
TX63544		407.51	39	17	
TX63547		311.43	87	32	3.1

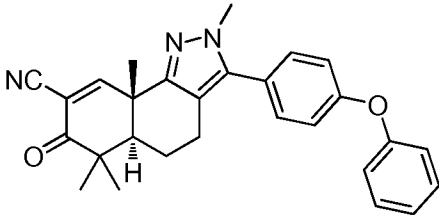
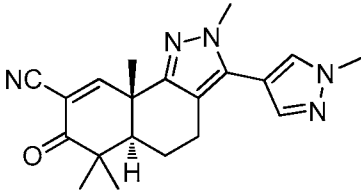
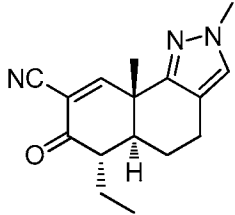
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63550		359.47	54	20	1.8
TX63551		255.32	49	18.1	
TX63552		343.43	24	8.9	1.9

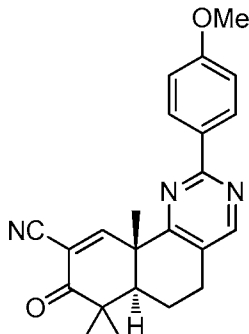
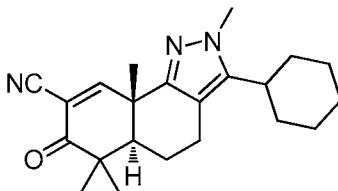
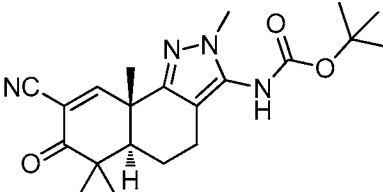
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63553		283.33	>200	--	
TX63554		267.33	42	15.6	1.9
TX63559		255.31	>200	--	
TX63561		323.44	44	15.7	2.4

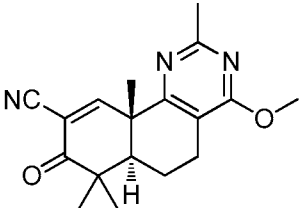
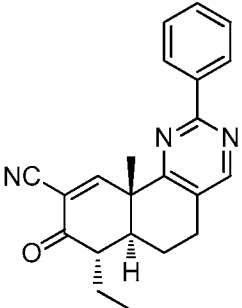
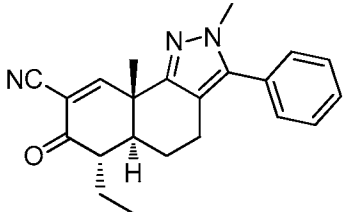
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63567		335.33	43	18.9	
TX63568		332.41	>200	--	1.3
TX63569		329.40	9.8	4.3	2.0

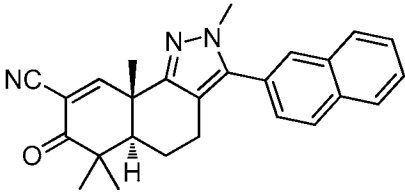
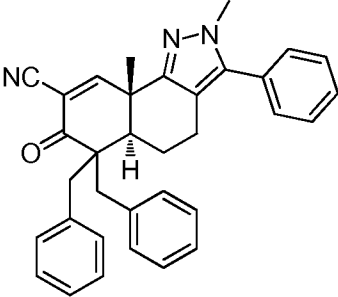
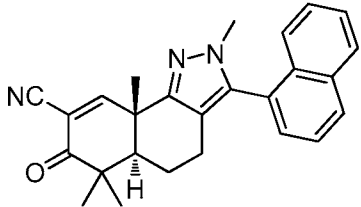
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63570		292.38	>200	--	
TX63578		290.36	>200	--	
TX63579		331.41	22	10.8	
TX63582		377.88	33	13	

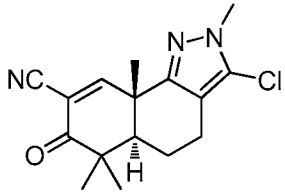
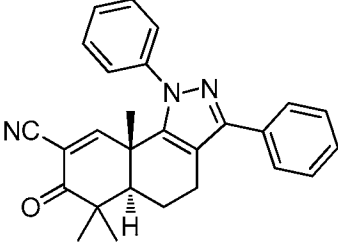
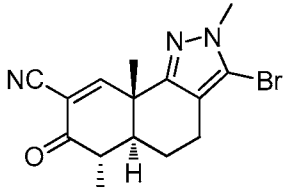
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63583		357.46	33	13	
TX63584		311.39	>200	--	3.1
TX63586		344.42	22	11	2.9

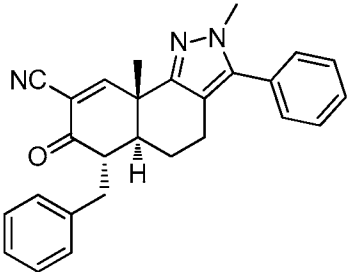
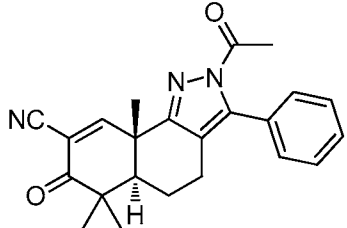
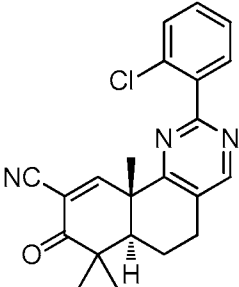
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63587		437.53	40	20	
TX63588		349.43	33	17	5.2
TX63589		269.35	44	22	

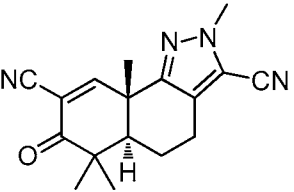
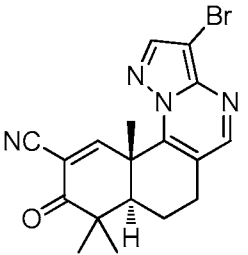
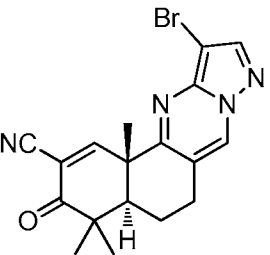
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63590		373.46	31	12.5	
TX63591		351.49	74	37	
TX63594		384.47	>200	--	

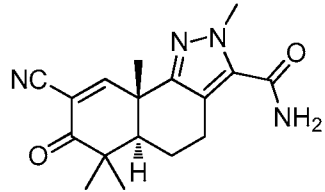
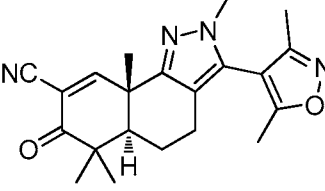
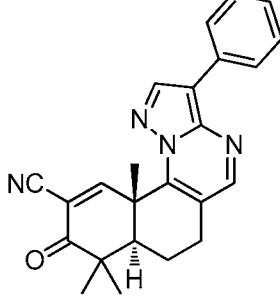
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63595		311.39	20	8.0	
TX63598		343.43	12	4.8	1.9
TX63599		345.45	14	5.8	3.2

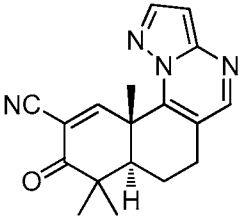
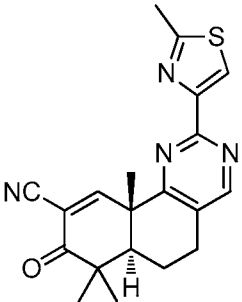
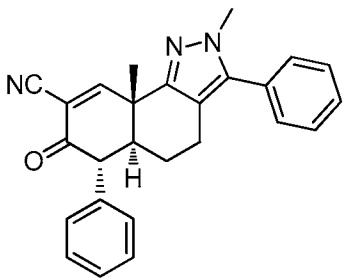
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63600		395.50	59	25	
TX63601		497.63	150	63	
TX63603		395.50	61	25	

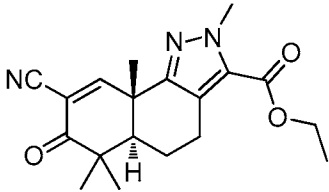
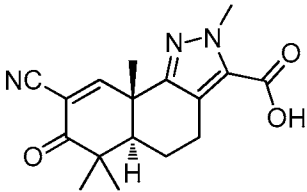
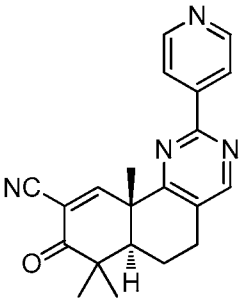
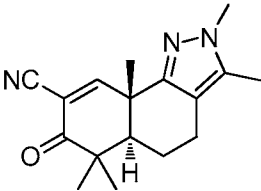
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			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
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TX63605		407.51	37	14.8	2.8
TX63606		334.22	11	4.6	

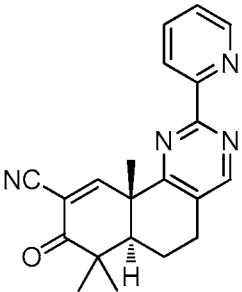
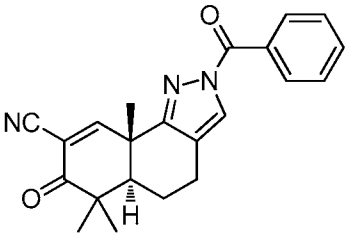
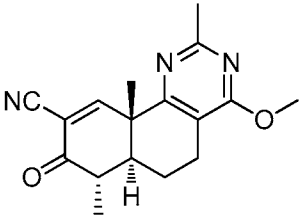
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			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63607		407.51	>200	--	1.0
TX63611		373.45	22	11	
TX63612		377.88	43	22	

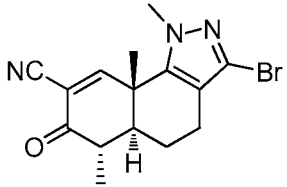
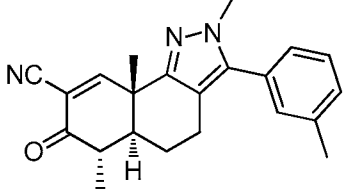
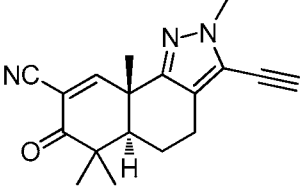
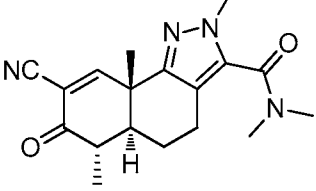
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			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63613		294.35	101	50	
TX63615		385.26	52	18	
TX63617		385.26	33	11	

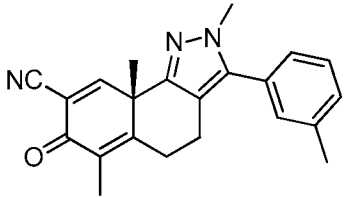
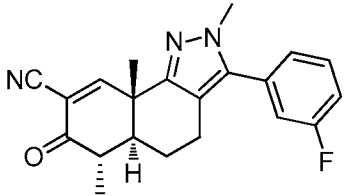
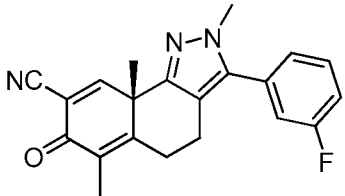
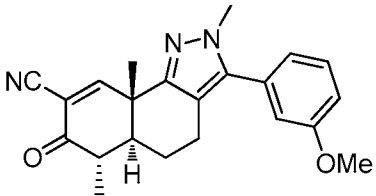
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63619		312.37	>200	--	
TX63625		364.44	77	59	
TX63626		382.46	38	29	

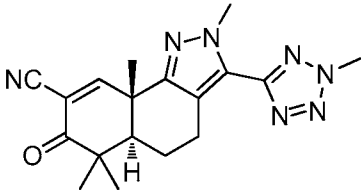
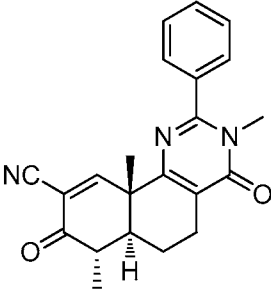
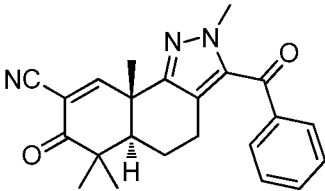
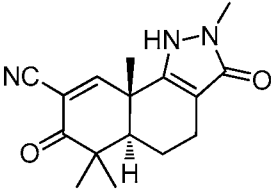
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63627		306.36	38	29	
TX63628		364.47	62	44	
TX63629		393.48	137	98	

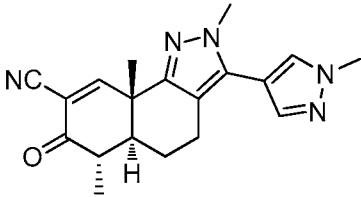
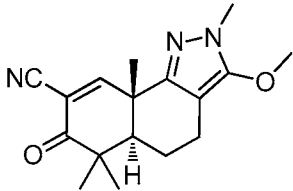
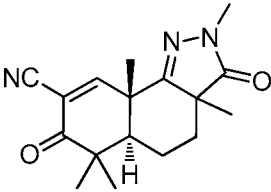
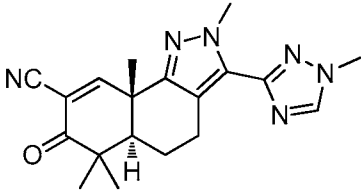
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			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63630		341.40	38	27	
TX63631		313.35	>200	--	
TX63636		344.42	27	14	
TX63637		283.37	45	35	

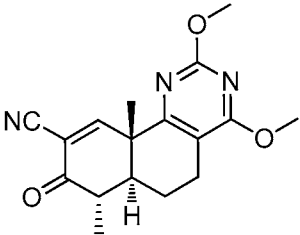
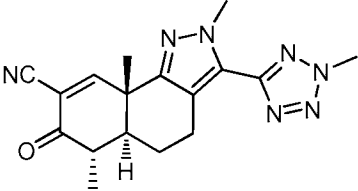
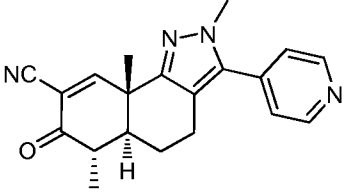
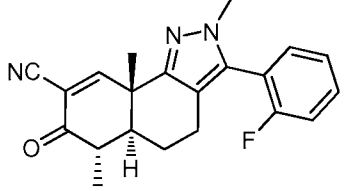
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			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63641		344.42	43	23	
TX63642		359.42	147	77	
TX63646		297.35	8.5	5.0	

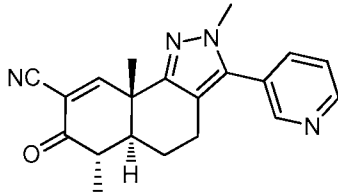
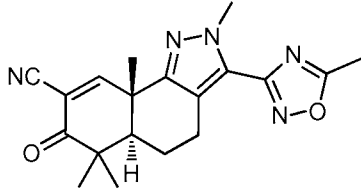
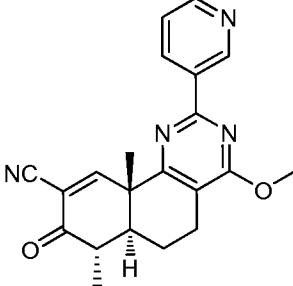
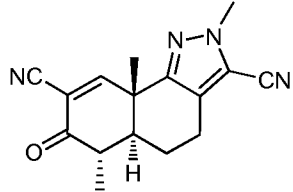
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			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63649		334.21	21	16	
TX63650		345.44	6.1	4.7	
TX63651		293.36	23	18	
TX63655		326.39	>200	--	

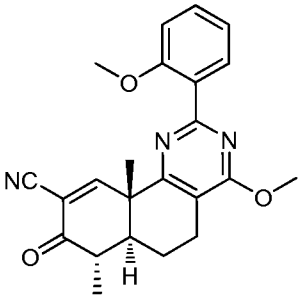
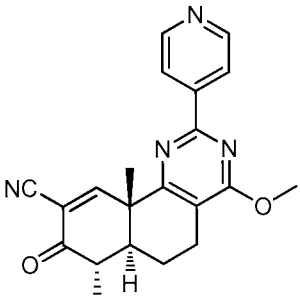
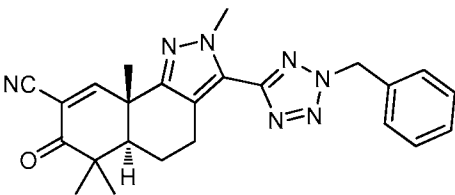
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			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63656		343.42	>200	--	
TX63659		349.41	8.1	6.2	
TX63663		347.39	108	63.5	
TX63664		361.44	8	4.0	

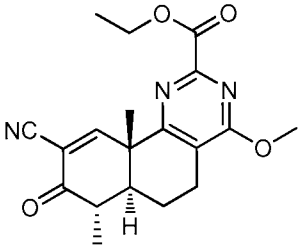
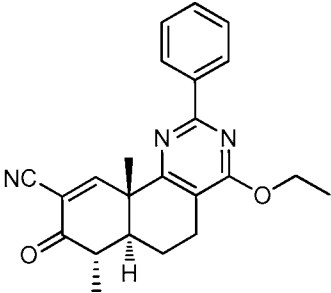
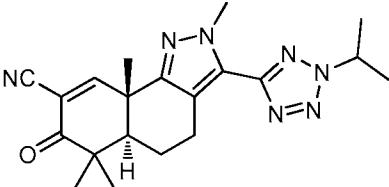
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63665		351.41	14	7.0	
TX63666		359.42	25	12.5	
TX63667		373.45	155	91	
TX63676		285.34	>200	--	

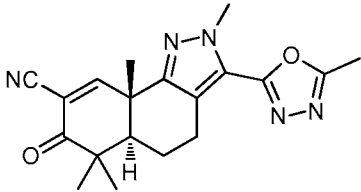
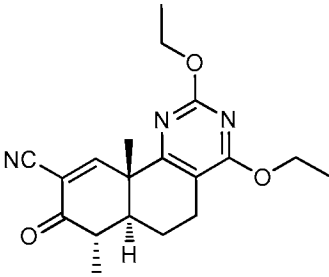
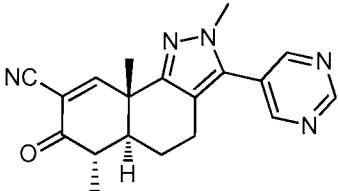
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63690		335.41	11	6.5	
TX93691		299.37	62	36.5	
TX63692		299.37	>200	--	
TX63714		350.42	>200	--	

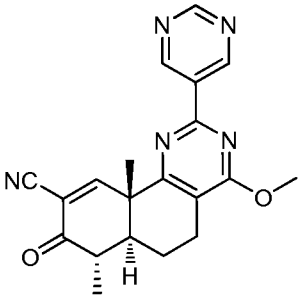
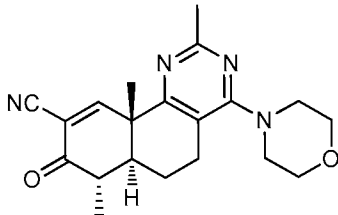
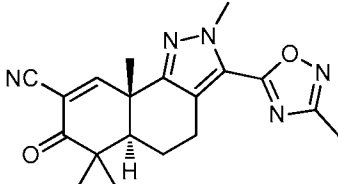
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63718		313.35	6	4.3	
TX63719		337.38	5.9	3.9	
TX63720		332.40	4.9	3.1	
TX63721		349.40	7.8	4.9	

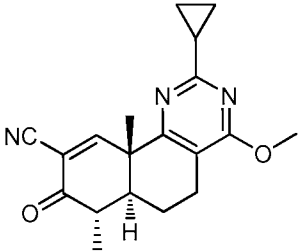
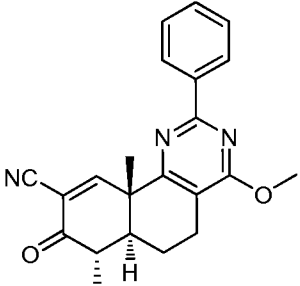
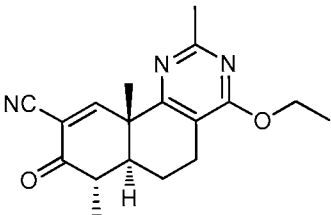
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63722		332.40	8.3	5.2	
TX63723		351.40	35	23.3	
TX63724		360.41	3.1	2.1	4.9
TX63725		280.32	24	16	

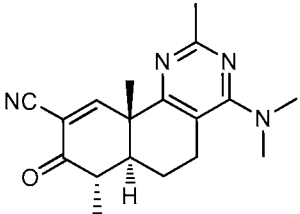
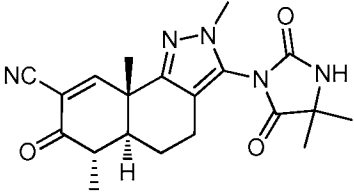
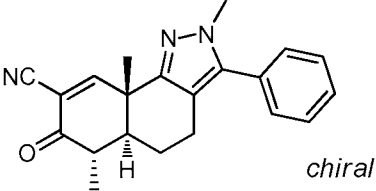
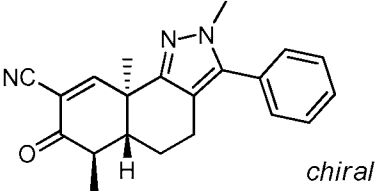
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63727		389.45	11.5	4.6	
TX63728		360.41	6.7	2.7	
TX63729		427.50	29	11.5	

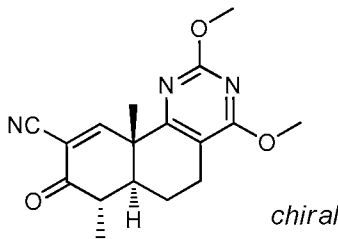
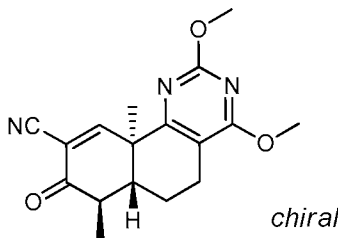
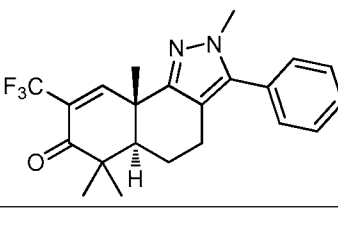
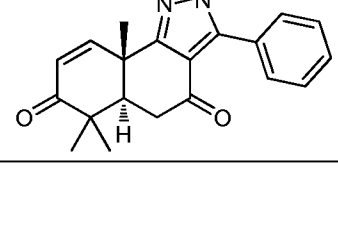
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63730		355.39	16	6.4	
TX63731		373.45	32	12.9	
TX63734		379.46	43	37	

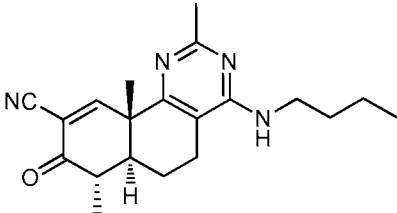
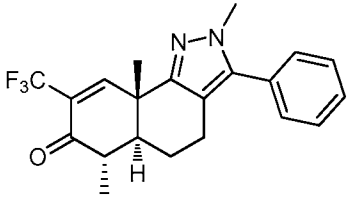
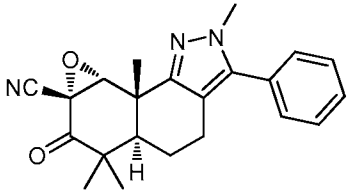
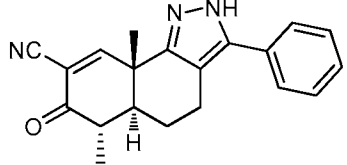
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63735		351.40	15.6	13	
TX63736		341.40	9.8	5.3	
TX63748		333.39	23	16.5	

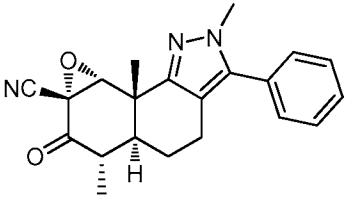
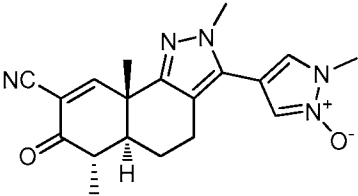
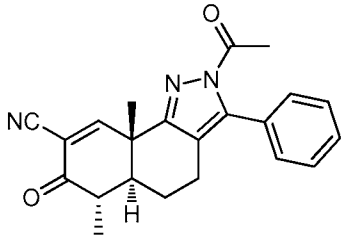
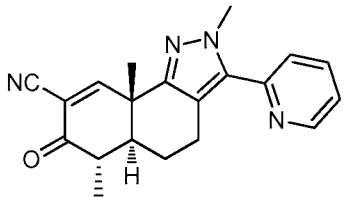
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
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TX63758		352.44	55	44	
TX63760		351.40	6.2	4.8	

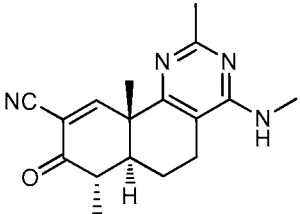
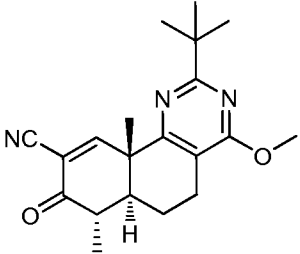
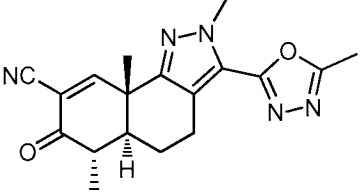
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63761		323.39	8.9	7.2	
TX63769		359.42	9.4	7.6	
TX63773		311.38	6	4.9	

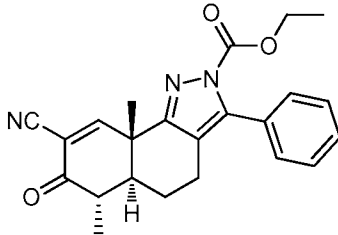
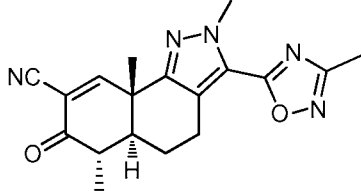
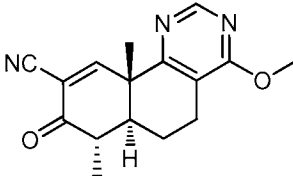
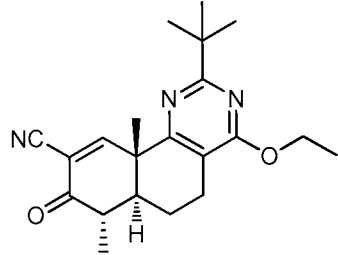
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63774		310.40	26.7	21.5	
TX63776		381.43	>200	--	
TX63791		331.41	2.3	1.4	
TX63792		331.41	147	95	

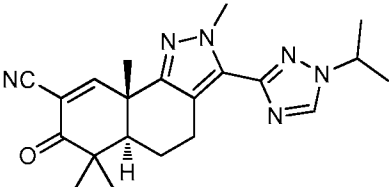
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63793	 <chem>COC1=CN=C(OC)C=C1[C@H]2C=CC(=O)C(C#N)C2</chem> <i>chiral</i>	313.35	2.5	2.0	
TX63794	 <chem>COC1=CN=C(OC)C=C1[C@H]2C=CC(=O)C(C#N)C2</chem> <i>chiral</i>	313.35	88.5	69	
TX63803	 <chem>CN1C=NC=C1[C@H]2C=CC(=O)C(C#N)C2</chem> <i>chiral</i>	388.43	50	43	
TX63804	 <chem>CN1C=NC=C1[C@H]2C=CC(=O)C(C#N)C2</chem> <i>chiral</i>	334.41	>200	--	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63827		338.45	59	47	
TX63829		374.40	22	18	
TX63834		361.44	105	83	
TX63836		317.39	6.1	4.8	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63848		347.41	9.5	5.7	
TX63849		351.41	>200	--	
TX63850		359.42	8.9	5.3	
TX63851		332.40	5.1	3.0	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63852		296.37	30	18	
TX63853		339.44	31	18.6	
TX63857		337.38	6.3	5.1	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63871		389.45	7.5	4.5	
TX63872		337.38	4.6	2.8	
TX63874		283.33	5.5	4.8	
TX63900		353.47	40	26	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC ₅₀ (nM)	Relative NO IC ₅₀	Fold induction at 62.5 nM
TX63905		378.47	129	85	

IV. 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. Based at least on the evidence presented above, the compounds of this invention may be used in the treatment or prevention of inflammation or diseases associated with inflammation.

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 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.

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), which are all incorporated herein by reference.

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 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. 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, 5 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, which are all incorporated by reference herein. 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 10 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 15 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 20 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 25 inflammatory pain and/or neuropathic pain, for example, by inducing Nrf2 and/or inhibiting NF- κ B.

In some embodiments, the compounds disclosed herein may be used in the treatment and prevention of diseases such as cancer, inflammation, Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism, amyotrophic lateral sclerosis, 30 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- κ B 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 inflammatory event to revert to a non-inflammatory state by promoting the resolution of inflammation and limiting excessive tissue damage to the host.

V. Pharmaceutical Formulations and Routes of Administration

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
5 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
10 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, 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 (Strejan *et al.*, 1984).

15 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.

20 Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. See for example U.S. Patent Application by J. Zhang, entitled "Amorphous Solid Dispersions of CDDO-Me for Delayed Release Oral Dosage Compositions," filed February 13,
25 2009, which is incorporated herein by reference. 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
30 (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.*, 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 humans, such as the model systems shown in the examples and drawings.

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 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.

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 $\pm 10\%$ 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 mg/kg/body weight to about 100 mg/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 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
5 and/or every evening, regardless of when the subject has eaten or will eat.

VI. 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
10 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
15 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
20 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
25 response to cancer, including (but not limited to) cancer vaccines. See Lu *et al.* (2011), which is incorporated herein by reference.

VII. 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
30 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.

Methods and Materials

5 **Nitric Oxide production and cell viability.** RAW264.7 mouse macrophages were plated in 96-well plates at 30,000 cells/well in triplicate in RPMI1640 + 0.5% FBS and incubated at 37°C with 5% CO₂. On the next day, cells were pre-treated with DMSO or drug (0-200nM dose range) for 2 hours, and then treated with recombinant mouse IFN γ (R&D Systems) for 24 hours. Nitric Oxide concentration in media was
10 determined using the Griess reagent system (Promega). Cell viability was determined using WST-1 reagent (Roche). IC₅₀ values were determined based on the suppression of IFN γ induced Nitric Oxide production normalized to cell viability.

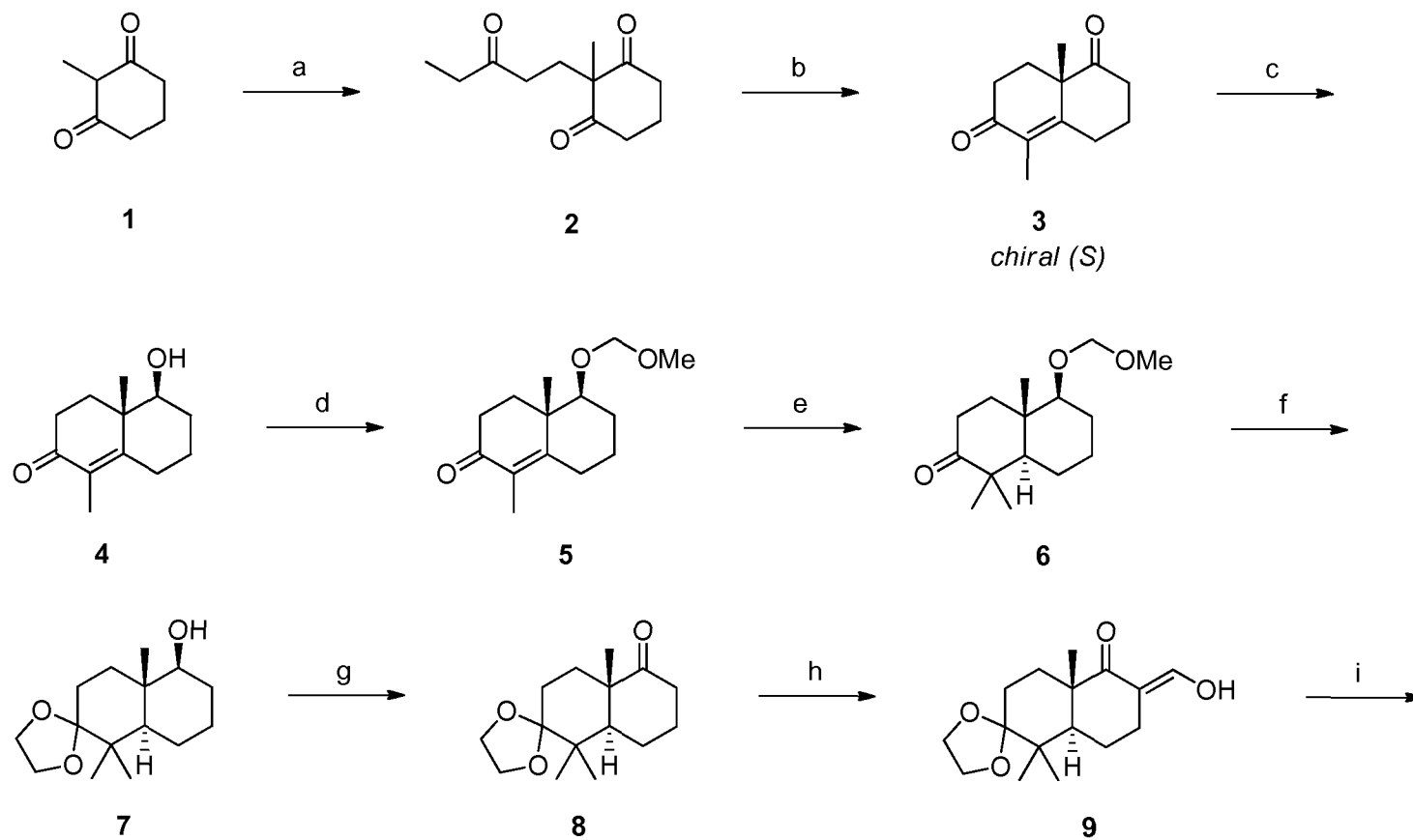
NQO1-ARE Luciferase Reporter Assay. This assay allows for quantitative assessment of the endogenous activity of the Nrf2 transcription factor in cultured
15 mammalian cells. Expression of *Firefly* luciferase from NQO1-ARE luciferase reporter plasmid is controlled by binding of Nrf2 to a specific enhancer sequence corresponding to the antioxidant response element (ARE) that was identified in the promoter region of the human NADPH:quinone oxidoreductase 1 (*NQO1*) gene (Xie
 et al., 1995). The plasmid was constructed by inserting a sequence:

20 5'- CAGTCACAGTGACTCAGCAGAATCTG-3' (SEQ ID NO:1)
 encompassing the human NQO1-ARE into the pLuc-MCS vector using HindIII/XhoI cloning sites (GenScript Corp., Piscataway, NJ). The assay is performed in HuH7 cells maintained in DMEM (Invitrogen) supplemented with 10% FBS and 100U/ml (each) of penicillin and streptomycin. For the assay, cells are plated in 96-well plates
25 at 17,000 cells per well. Twenty four hours later, the cells are co-transfected with 50 ng each of NQO1-ARE reporter plasmid and pRL-TK plasmid using Lipofectamine 2000 transfection reagent (Invitrogen). pRL-TK plasmid constitutively expresses *Renilla* luciferase and is used as an internal control for normalization of transfection levels. Thirty hours after transfection, the cells are treated with compounds (at
30 concentrations ranging from 0 to 1 μ M) for eighteen hours. *Firefly* and *Renilla* luciferase activity is assayed by Dual-Glo Luciferase Assay (Promega Corp., Madison, WI), the luminescence signal is measured on an L-Max II luminometer (Molecular Devices). *Firefly* luciferase activity is normalized to the *Renilla* activity,

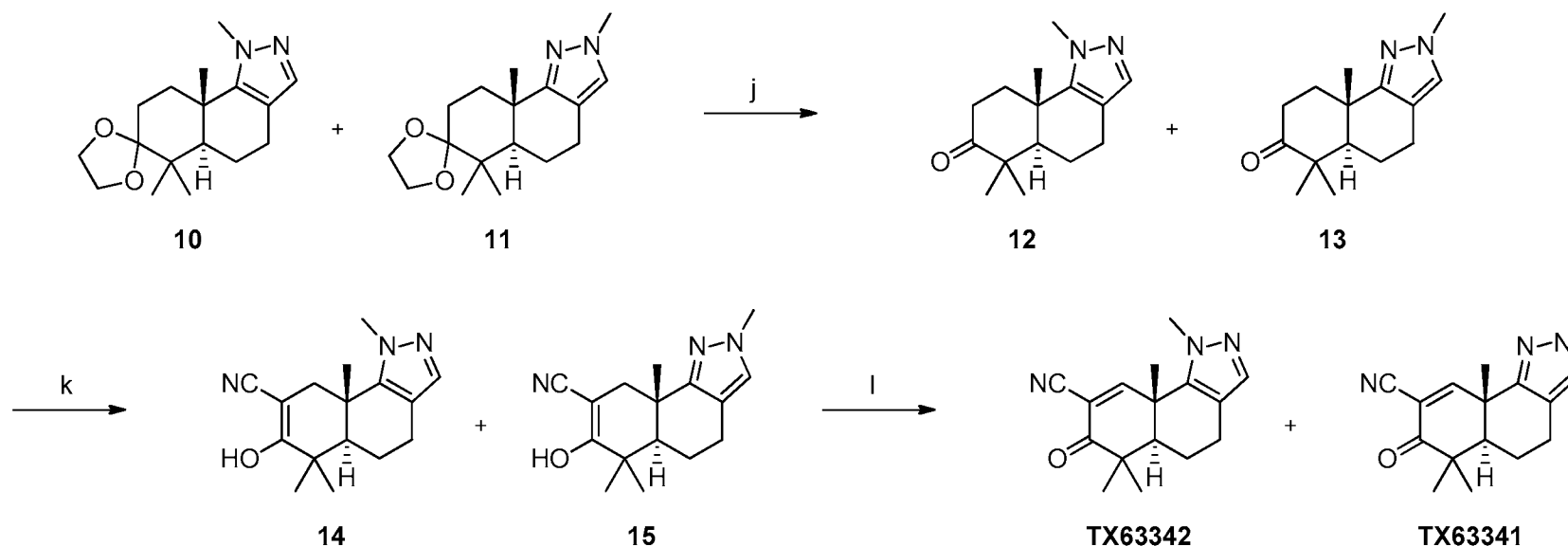
and fold induction over a vehicle control (DMSO) of normalized *Firefly* activity is calculated. The fold induction at 62.5 nM concentration is used for comparing relative potencies of compounds to induce Nrf2 transcriptional activity. See Xie T, Belinsky M, Xu Y, Jaiswal AK. ARE- and TRE-mediated regulation of gene
5 expression. Response to xenobiotics and antioxidants. *J Biol Chem.* (1995) 270(12):6894-6900, which is incorporated herein by reference.

Syntheses of Certain Synthetic AIM Compounds of the Present Disclosure

Scheme 1(a):

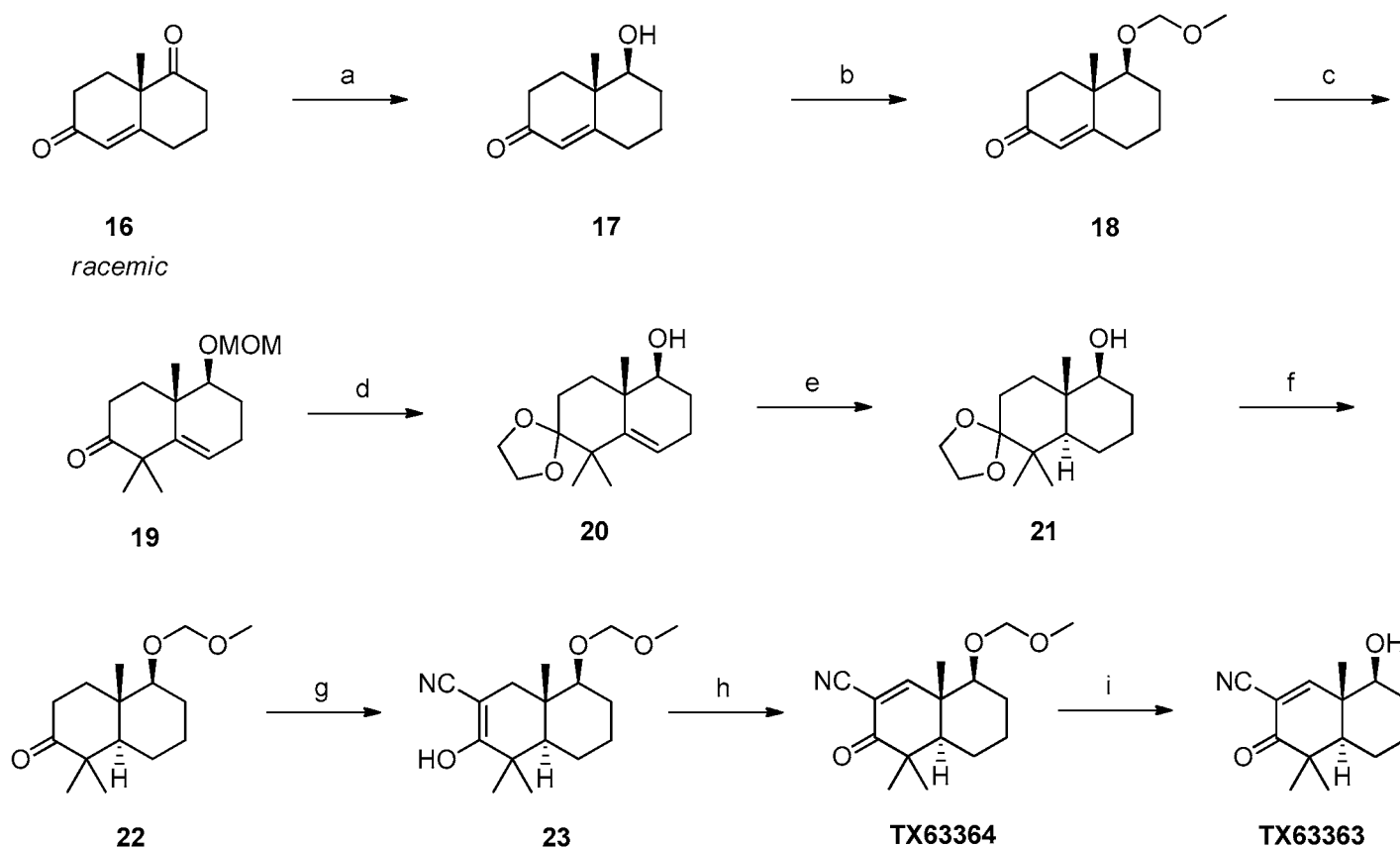


Scheme 1(b):



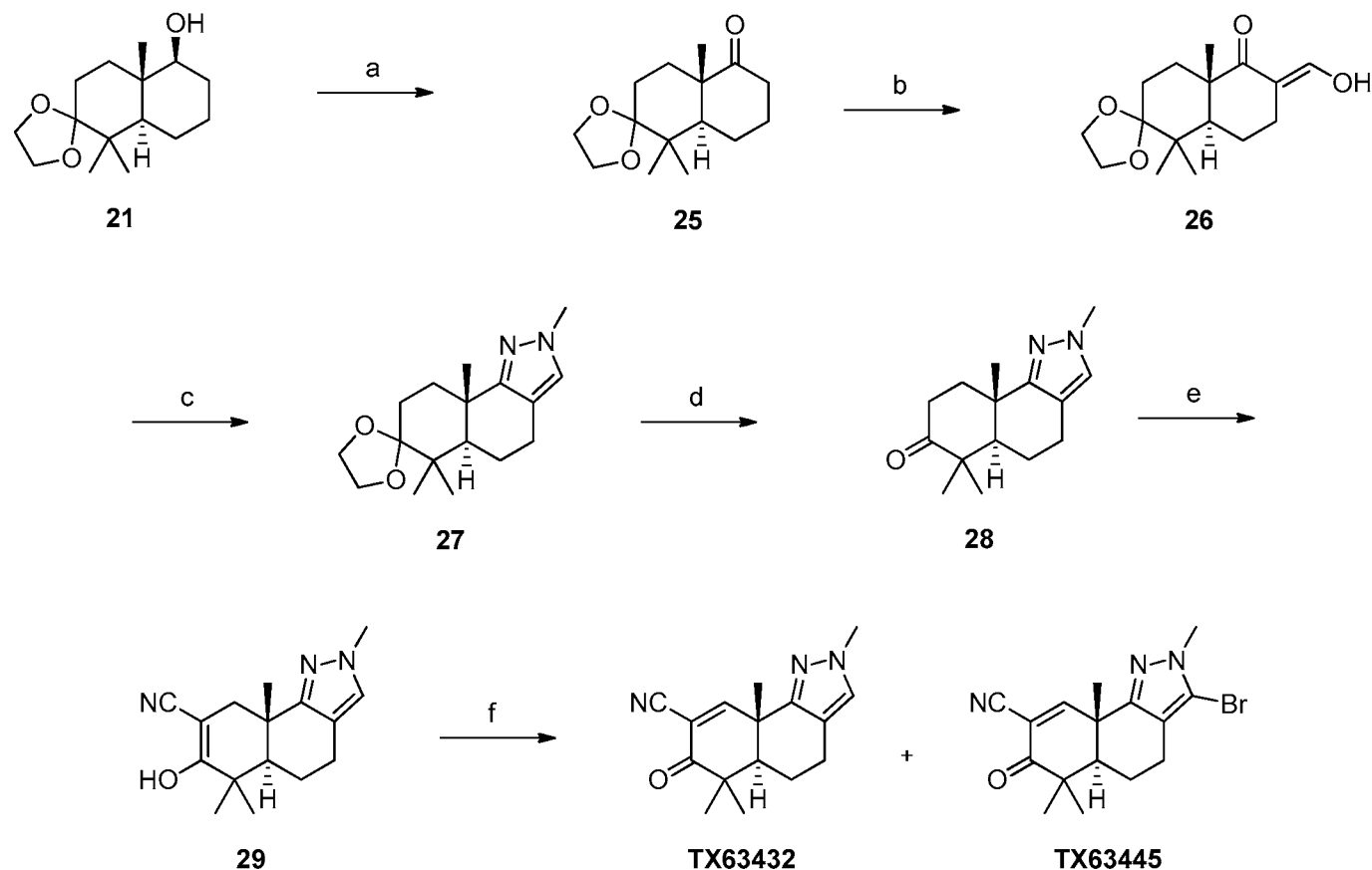
Reagents and conditions pertaining to Scheme 1(a) and 1(b): (a) Ethyl vinyl ketone, Et₃N, THF, 81%; (b) (*S*)-phenylalanine, CSA, DMF, RT to 70 °C, 5 d, 45%; (c) NaBH₄, EtOH, 0 °C, 1 h, 90%; (d) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, 3 d, 90%; (e) (i) Li, *t*-BuOH, NH₃, THF, reflux, 2h (ii) MeI, THF, -78 °C, 2h, 28%; (f) Ethylene glycol, 10-CSA, cyclohexane, -H₂O, 66%; (g) PDC, 95%; (h) HCO₂Et, NaOMe, 0 °C to rt, 90%; (i) MeNHNH₂, EtOH, 60 °C, 2 h, quantitative; (j) 3 N HCl(aq), MeOH, RT, 3h, 59%; (k) (i) LDA, THF, -78 °C, 45 min; (ii) TsCN, -78 °C, 45 min, 77%; (l) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 55 °C, 12 h, 23% **TX63342**; 9% **TX63341**.

Scheme 2:



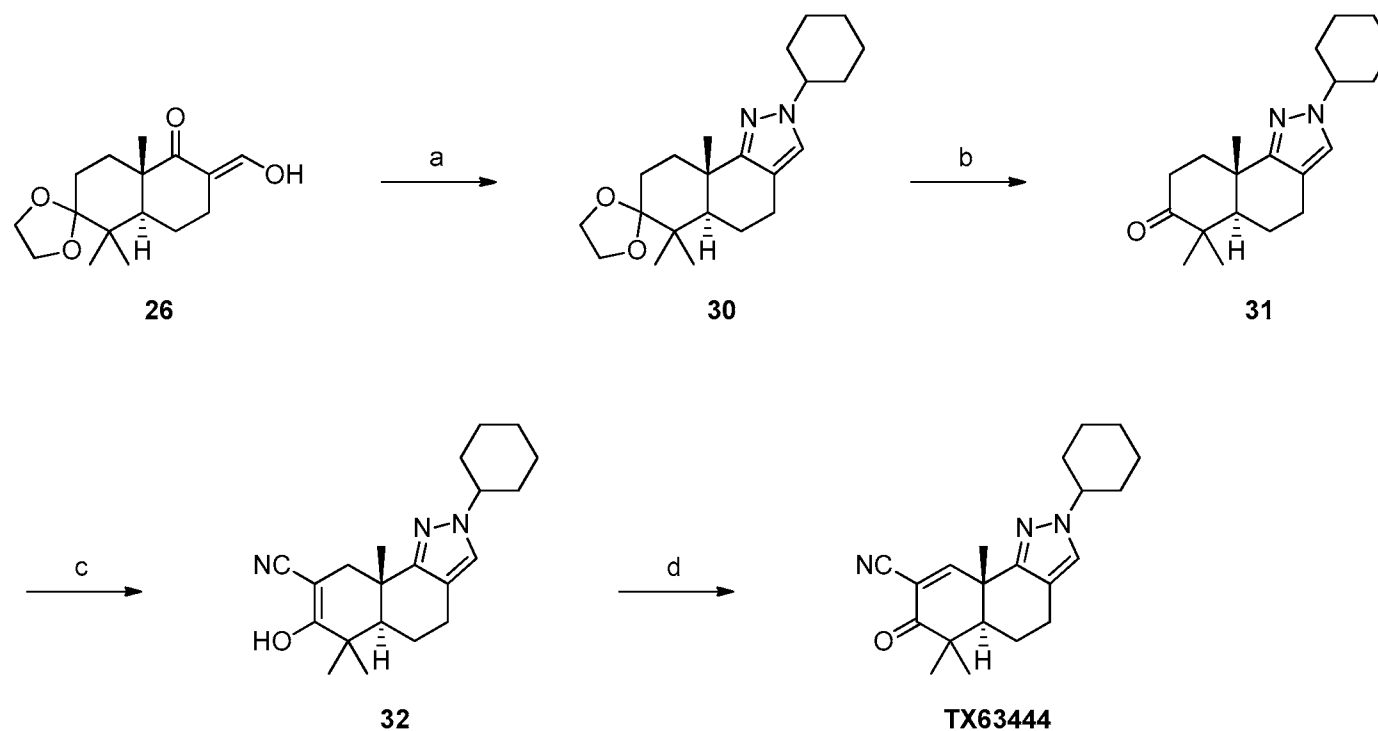
Reagents and conditions pertaining to Scheme 2: (a) NaBH_4 , EtOH, 0 °C, 92%; (b) MOM-Cl, *i*-Pr₂NEt, RT, 78%; (c) KO*t*-Bu, *t*-BuOH, MeI, 43%; (d) Ethylene glycol, *p*-TsOH·H₂O, toluene, −H₂O, 99%; (e) H₂, 10% Pd/C, EtOH, 99%; (f) MOM-Cl, *i*-Pr₂NEt, RT, 12 h, quantitative; (g) (i) LDA, THF, −78 °C, 30 min; (ii) TsCN, −78 °C, 30 min, 66%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 3 h, 0 °C; (ii) pyridine, 60 °C, 4 h, 86%; (i) 3 N HCl (aq), THF, RT, 2 d, 68%.

Scheme 3:



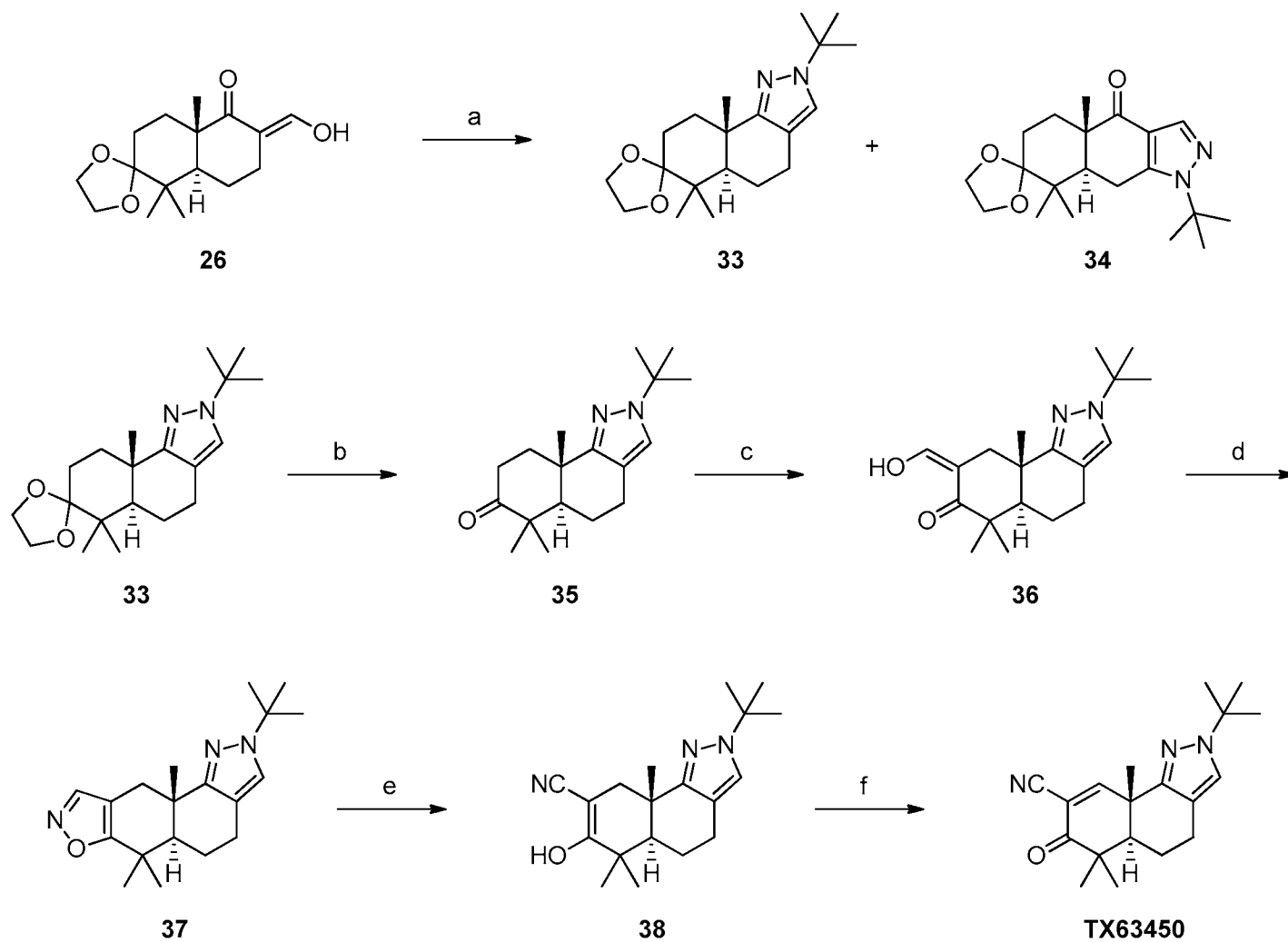
Reagents and conditions pertaining to Scheme 3: (a) PDC, 93% yield; (b) HCO₂Et, NaOMe, 0 °C to RT, quantitative; (c) MeNHNH₂, EtOH, 60 °C, 2 h, 97%; (d) 3 N HCl (aq), MeOH, RT, 3 h, 86%; (e) (i) LDA, THF, -78 °C, 45 min; (ii) TsCN, -78 °C, 45 min, 44%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, 0 °C; (ii) pyridine, 55 °C, **TX63432**: 29%, **TX63445**: 4%.

Scheme 4:



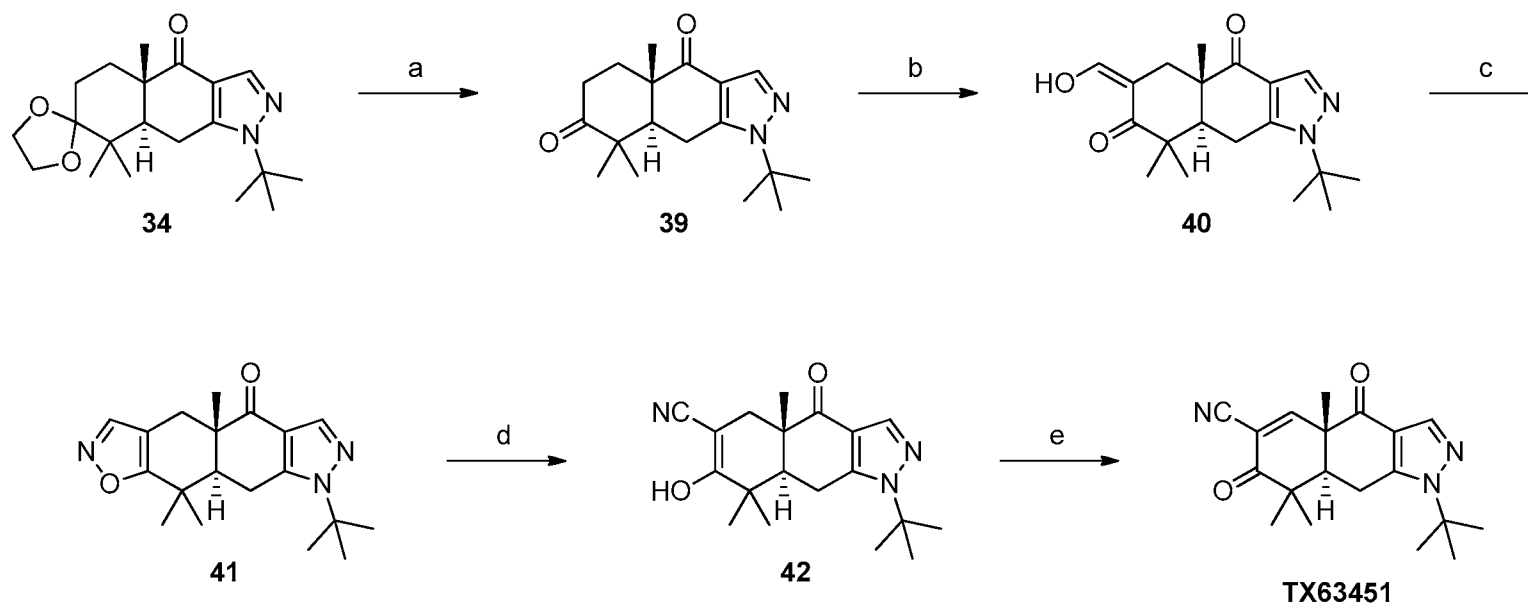
Reagents and conditions pertaining to Scheme 4: (a) Cyclohexylhydrazine-HCl, Et₃N, EtOH, 15 min, 36%; (b) 3 N HCl (aq), MeOH, rt, 3 h, 98% yield; (c) LDA, TsCN, THF, -78 °C, 1.5 h, 46% yield; (d) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 55 °C, 16 h, 59% yield.

Scheme 5:



Reagents and conditions pertaining to Scheme 5: (a) *t*-BuNHNH₂-HCl, Et₃N, EtOH, reflux, 5 h; RT, 12 h, 35% compound **36**; 36% compound **37**; (b) 1 N HCl (aq), MeOH, RT, 12 h, quantitative; (c) HCO₂Et, NaOMe, RT, 12 h, 90%; (d) NH₂OH-HCl, 50 °C, 12 h, quantitative; (e) NaOMe, 55 °C, 5.5 h; RT, 12 h, 59%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, time; (ii) pyridine, 50 °C, 12 h, 56%.

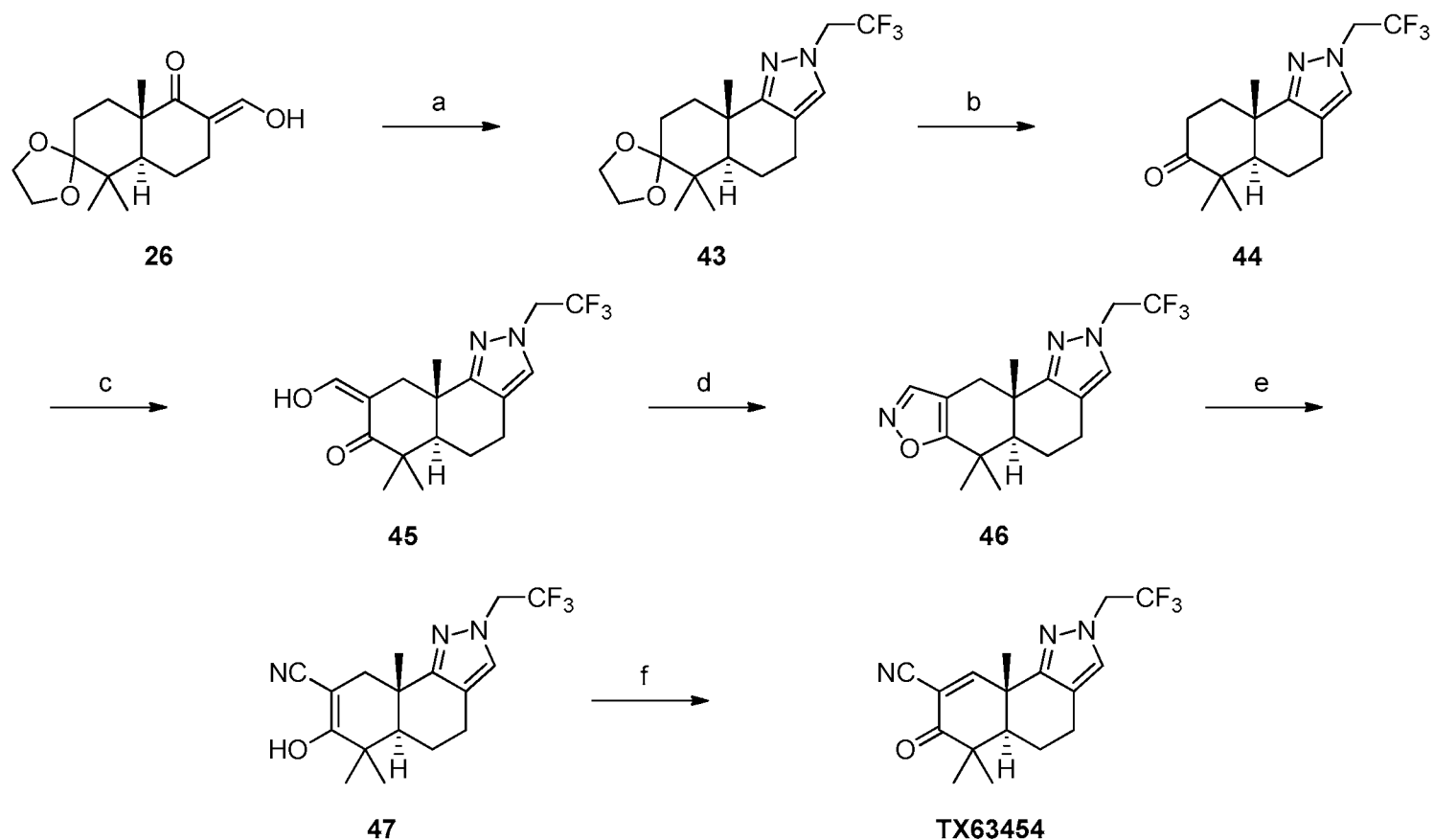
Scheme 6:



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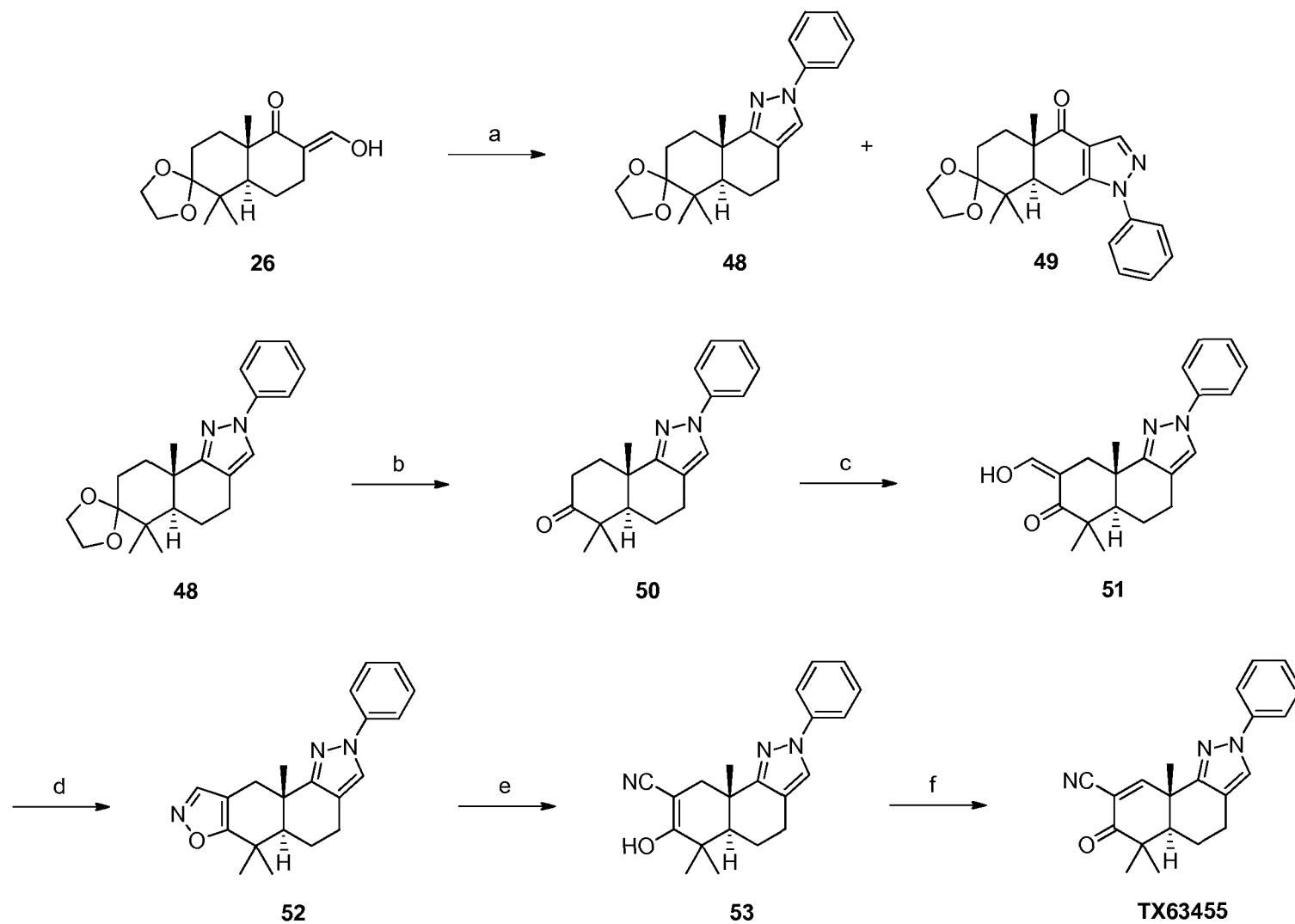
Reagents and conditions pertaining to Scheme 6: (a) 1 N HCl (aq), MeOH, RT, 12 h, 86%; (b) HCO₂Et, NaOMe, RT, 12 h, 83%; (c) NH₂OH-HCl, 50 °C, 12 h, quantitative; (d) NaOMe, 55 °C, 5.5 h; RT, 12 h, 80%; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, time; (ii) pyridine, 50 °C, 12 h, 67%.

Scheme 7:



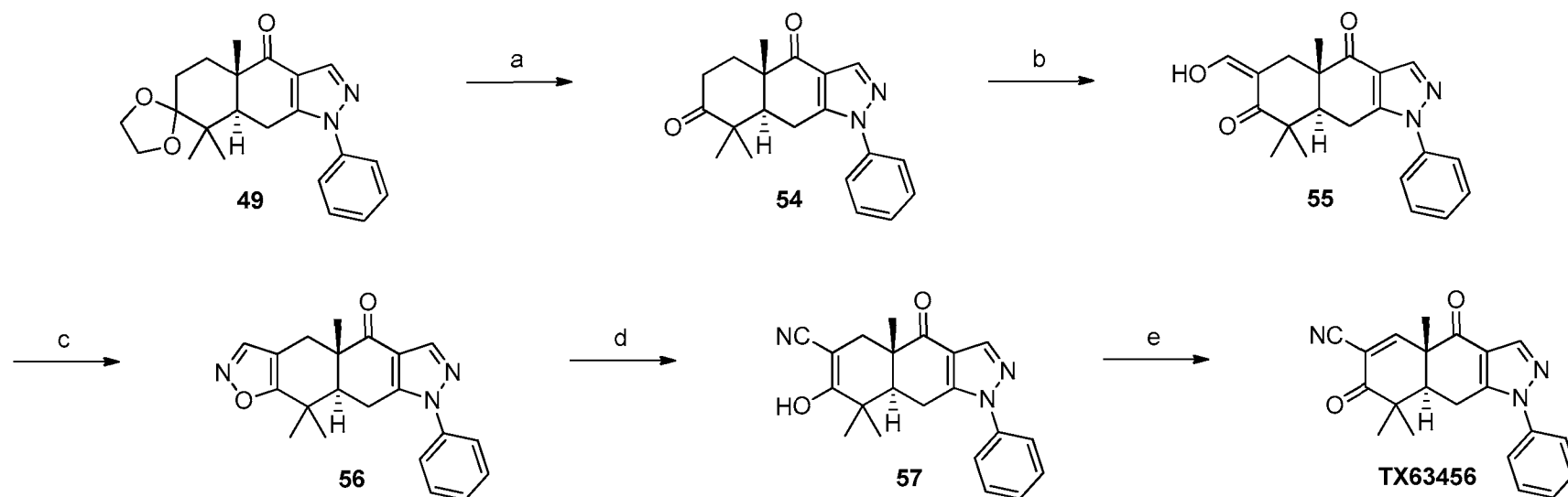
Reagents and conditions pertaining to Scheme 7: (a) (2,2,2-trifluoroethyl)hydrazine, EtOH, 60 °C, 2 h, 70% (b) 3 N HCl (aq), MeOH, RT, 12 h, quantitative; (c) HCO₂Et, NaOMe, RT, 12 h, 96%; (d) NH₂OH-HCl, 50 °C, 12 h, 93%; (e) NaOMe, 50 °C, 6 h, 52%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 54%.

Scheme 8:



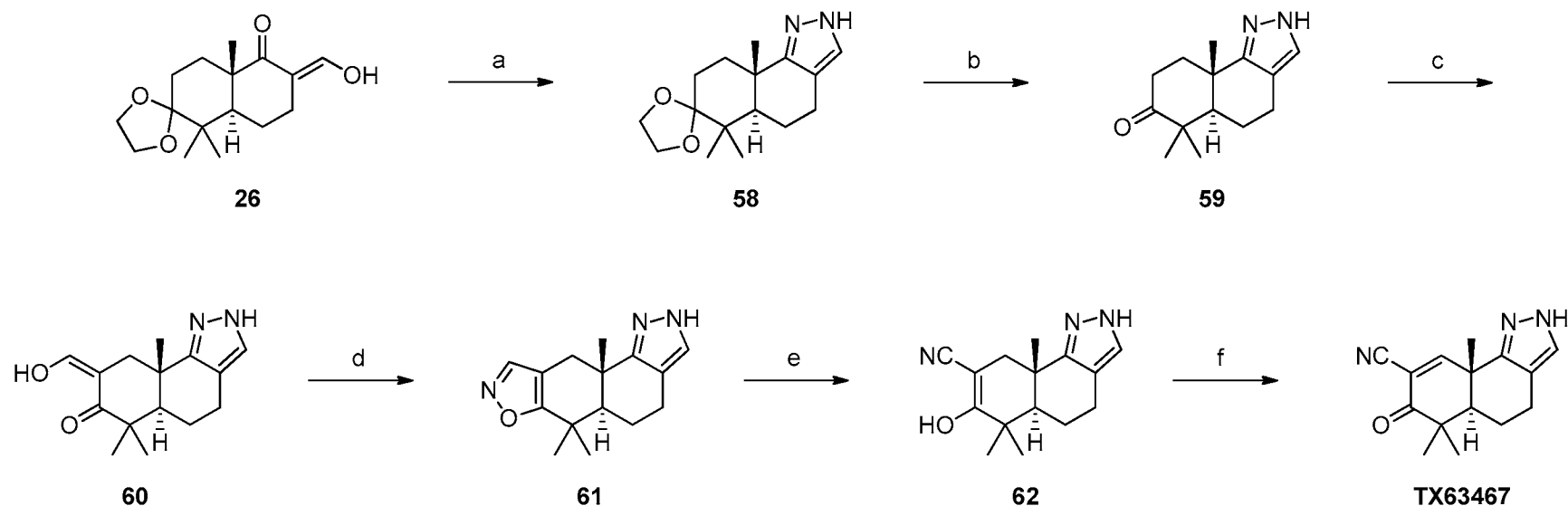
Reagents and conditions pertaining to Scheme 8: (a) Phenylhydrazine-HCl, NaOAc-3H₂O, EtOH, 70 °C, 12 h, 35% compound **51**; 51% compound **52**; (b) 1 N HCl (aq), MeOH, RT, 12 h, 92%; (c) HCO₂Et, NaOMe, RT, 12 h, 97%; (d) NH₂OH-HCl, 50 °C, 12 h, 91%; (e) NaOMe, 55 °C, 5.5 h; RT, 12 h, 80%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, time; (ii) pyridine, 50 °C, 12 h, 3%.

Scheme 9:



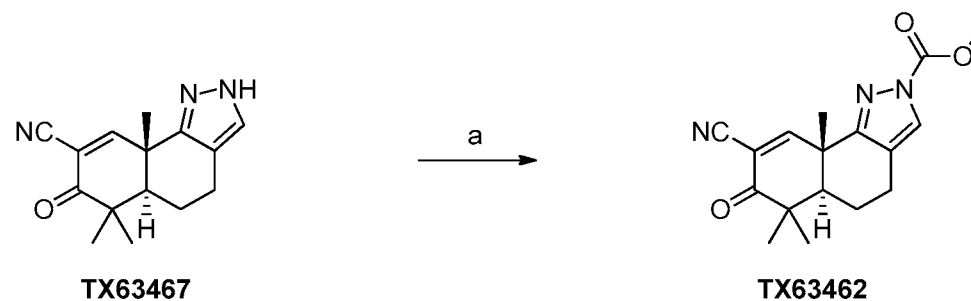
Reagents and conditions pertaining to Scheme 9: (a) 1 N HCl (aq), MeOH, RT, 12 h, 92%; (b) HCO₂Et, NaOMe, RT, 12 h, 95%; (c) NH₂OH-HCl, 50 °C, 12 h, 76%; (d) NaOMe, 55 °C, 5.5 h; RT, 12 h, 79%; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, time; (ii) pyridine, 50 °C, 12 h, 24%.

Scheme 10:



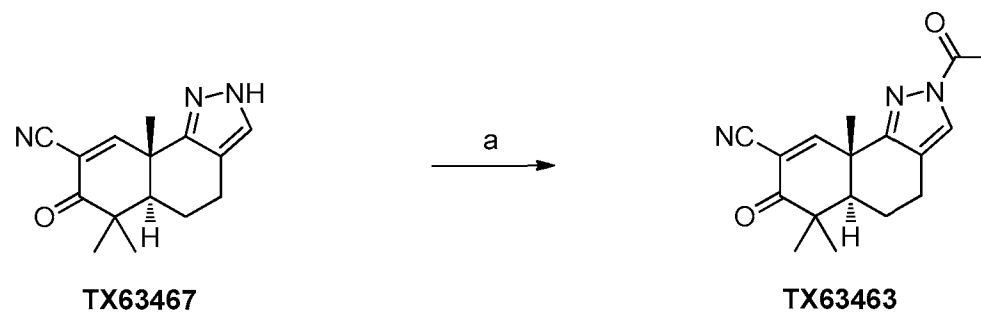
Reagents and conditions pertaining to Scheme 10: (a) hydrazine, EtOH, r.t, 1 h; 60 °C, 1 h, 82%; (b) 1 N HCl (aq), MeOH, RT, 12 h, quantitative; (c) HCO₂Et, NaOMe, RT, 12 h, 99%; (d) NH₂OH-HCl, 50 °C, 12 h, 97%; (e) NaOMe, 55 °C, 5.5 h; RT, 12 h, 83%; (f) (i) DDQ, benzene, reflux, 4.5 h, 43%.

Scheme 11:



Reagents and conditions pertaining to Scheme 11: (a) AcCl, NaHCO₃ (aq), THF, 0 °C, 1 h, 16%.

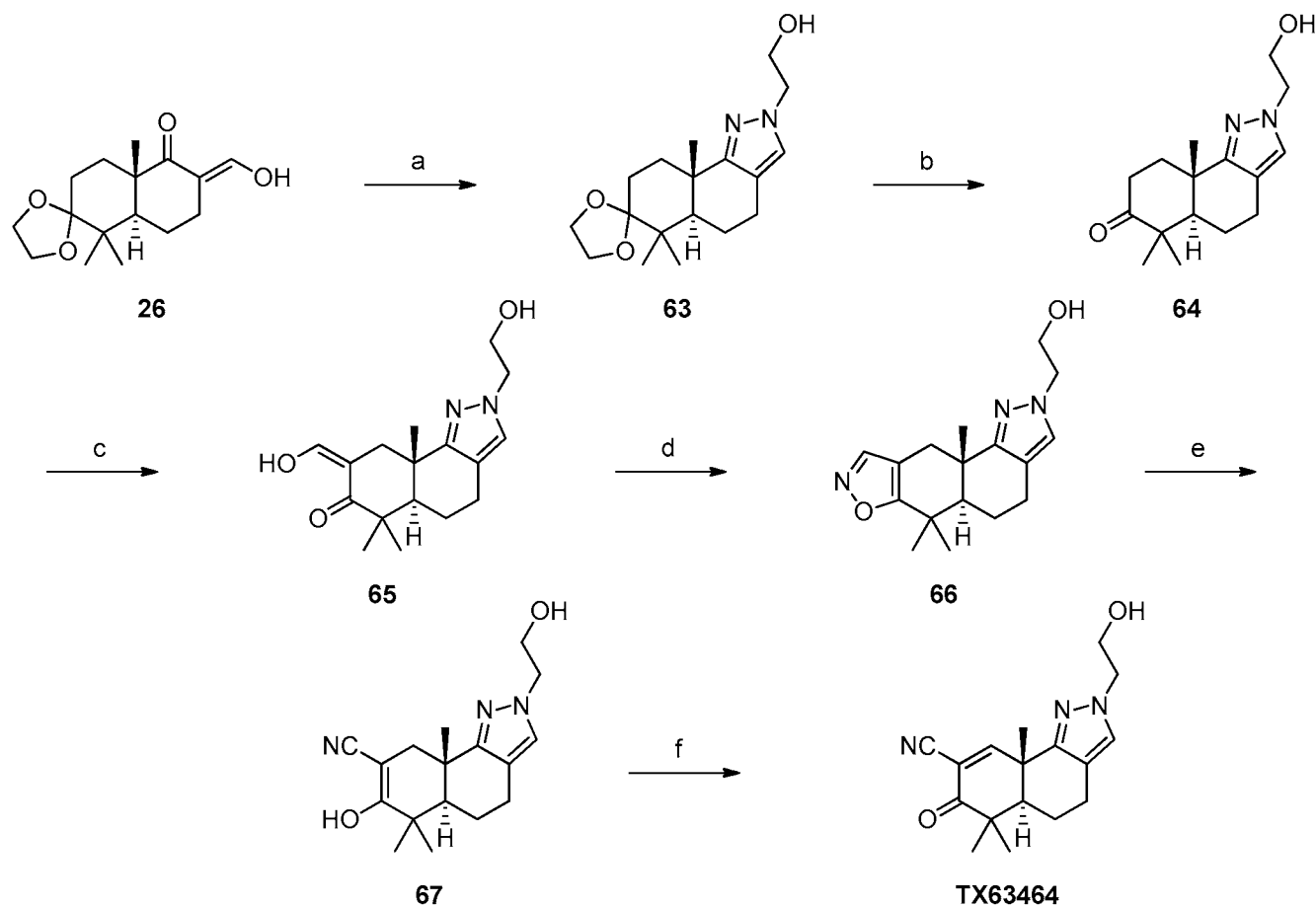
Scheme 12:



5

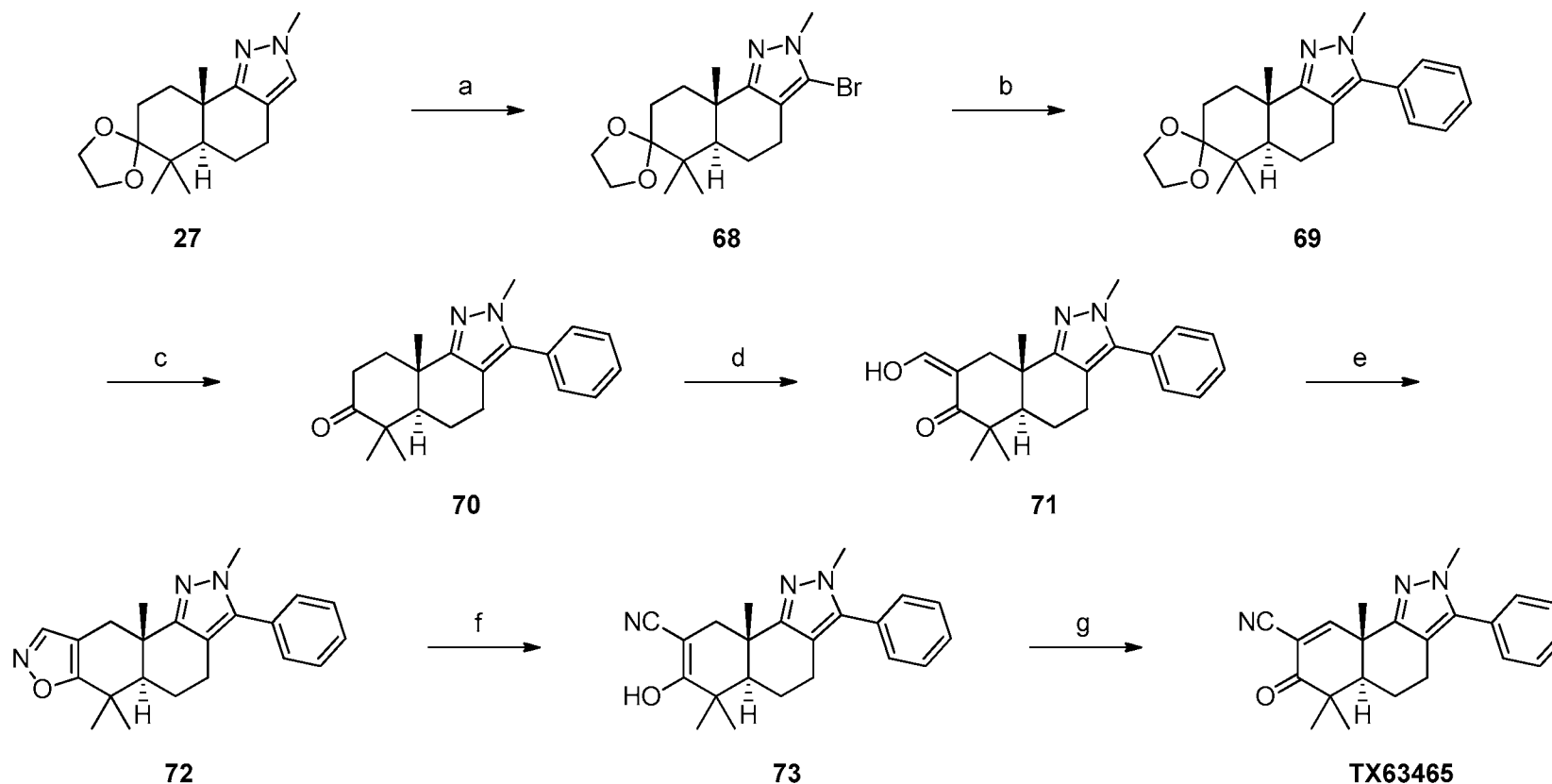
Reagents and conditions pertaining to Scheme 12: (a) AcCl, NaHCO₃ (aq), THF, 0 °C, 1 h, 24%.

Scheme 13:



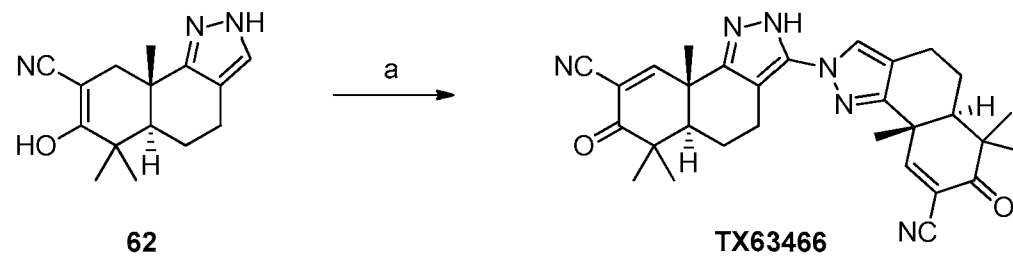
Reagents and conditions pertaining to Scheme 13: (a) 2-hydrazinylethanol, EtOH, 60 °C, 2 h, 93% (b) 3N HCl (aq), MeOH, RT, 12 h, 62%; (c) HCO₂Et, NaOMe, RT, 12 h, 91%; (d) NH₂OH-HCl, 50 °C, 12 h, quantitative; (e) NaOMe, 50 °C, 6 h, quantitative; (f) (i) pyridinium bromide perbromide, dioxane, RT, 2 h; (ii) pyridine, 50 °C, 12 h, 5%.

Scheme 14:



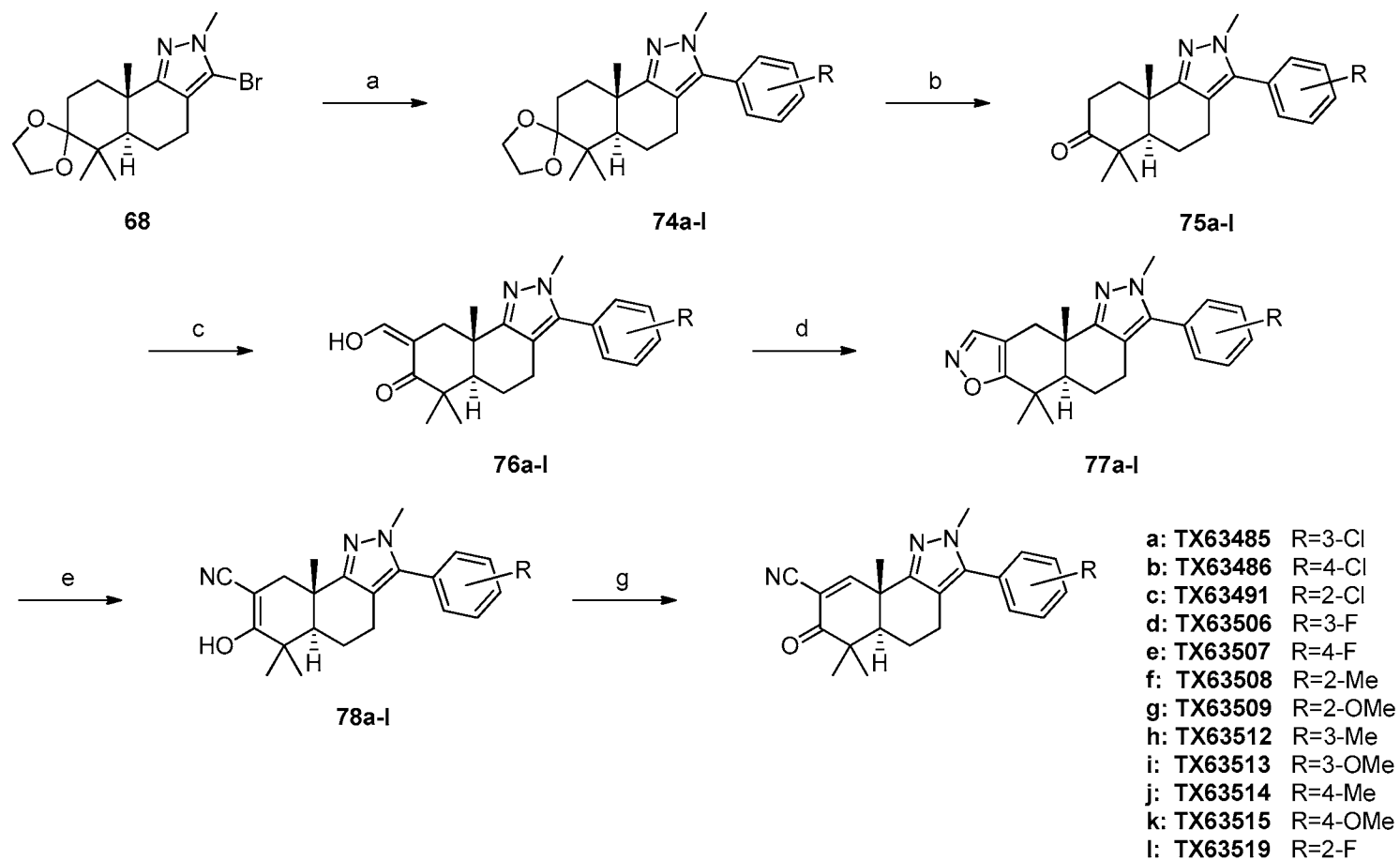
Reagents and conditions pertaining to Scheme 14: (a) 1,3-dibromo-5,5-dimethylhydantoin, CH_2Cl_2 , RT, 3 h, 54% (b) phenylboronic acid, $\text{Pd}(\text{OAc})_2$, Ph_3P , K_3PO_4 , DME, 85 °C, 9 h, 53%; (c) 3 N HCl (aq), MeOH, RT, 12 h, quantitative; (d) HCO_2Et , NaOMe, RT, 12 h, 92%; (e) 5 $\text{NH}_2\text{OH}\cdot\text{HCl}$, 50 °C, 12 h, 96%; (f) NaOMe, 50 °C, 6 h, 75%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 69%.

Scheme 15:



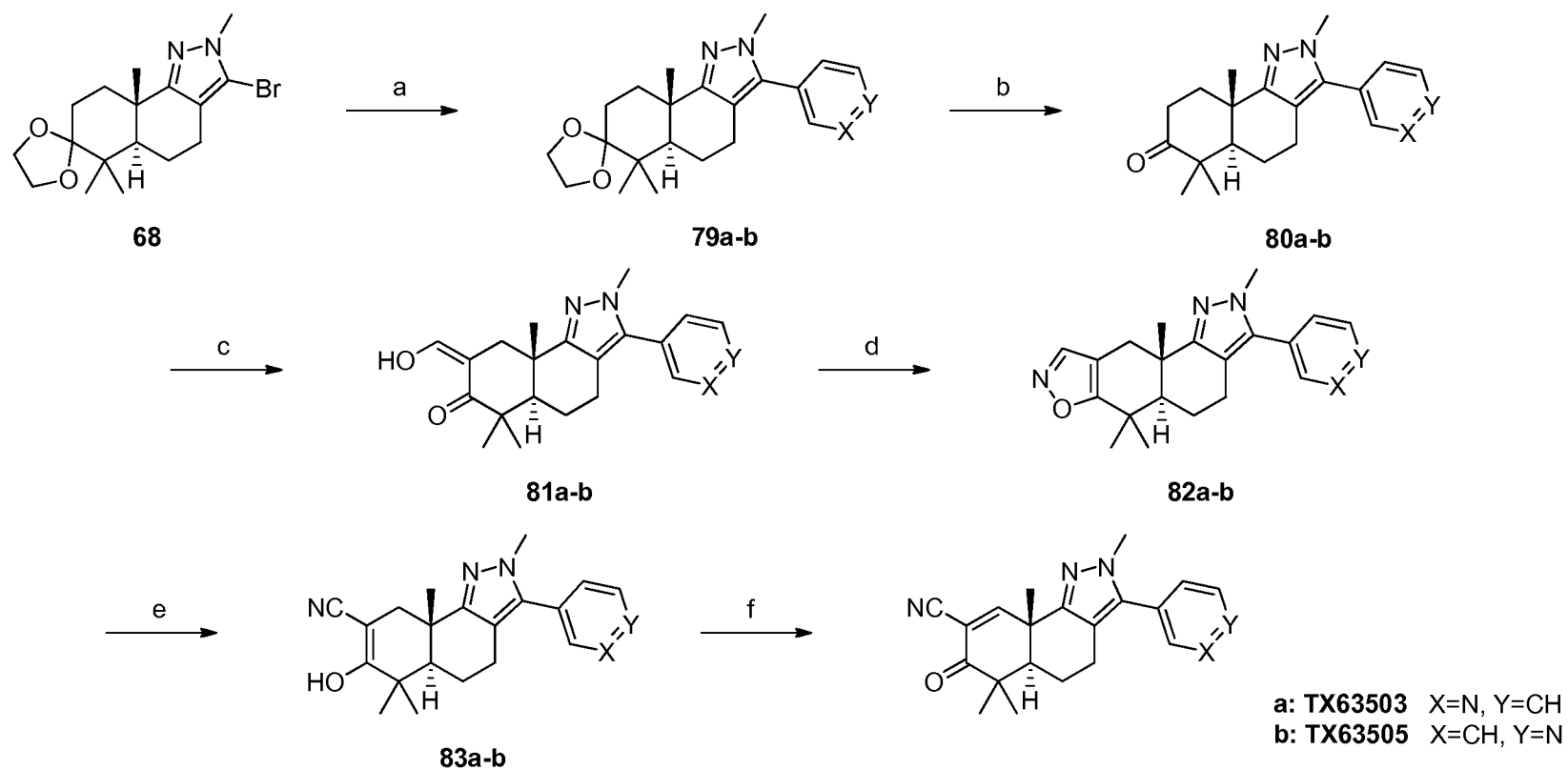
Reagents and conditions pertaining to Scheme 15 (a) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 6%.

Scheme 16:



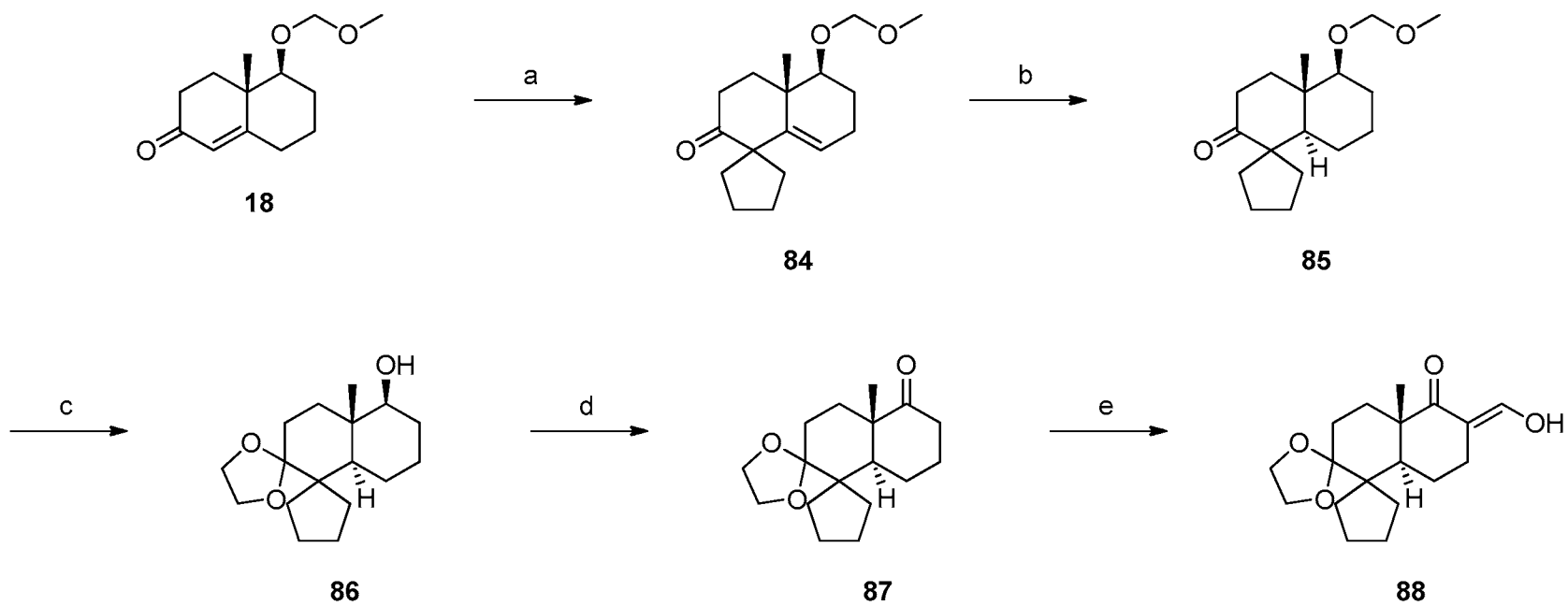
Reagents and conditions pertaining to Scheme 16: (a) arylboronic acid, Pd(OAc)₂, Ph₃P, K₃PO₄, DME, 85 °C, 9 h, yields; (b) 3 N HCl (aq), MeOH, RT, 12 h, yields; (c) HCO₂Et, NaOMe, RT, 12 h, yields; (d) NH₂OH-HCl, 50 °C, 12 h, yields; (e) NaOMe, 50 °C, 6 h, yields; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, yields.

Scheme 17:

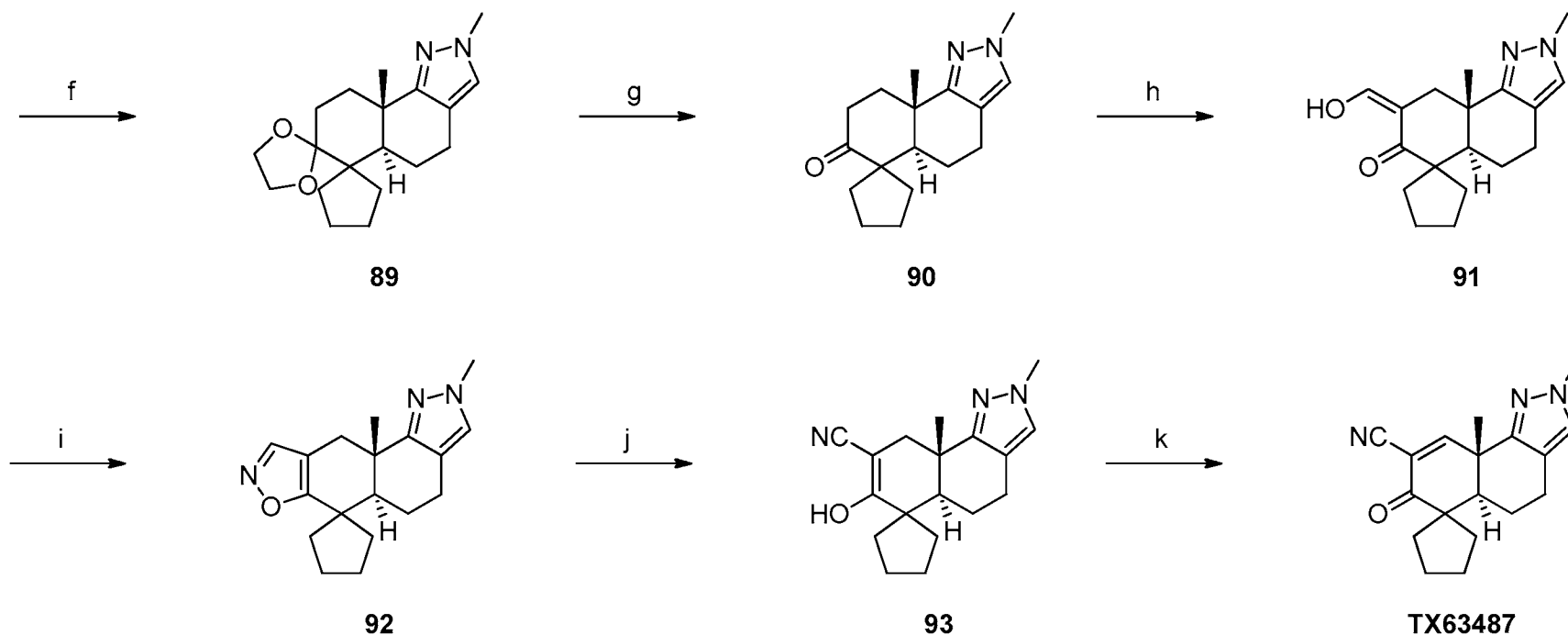


Reagents and conditions pertaining to Scheme 17: (a) 3- or 4-pyridinylboronic acid, Pd(OAc)₂, Ph₃P, K₃PO₄, DME, 85 °C, 9 h, **83a**: 26%, **83b**: 49%; (b) 3 N HCl (aq), MeOH, RT, 12 h, **84a**: 97%, **84b**: quantitative; (c) HCO₂Et, NaOMe, RT, 12 h, **85a**: quantitative, **85b**: quantitative; (d) NH₂OH-HCl, 50 °C, 12 h, **86a**: quantitative, **86b**: quantitative; (e) NaOMe, 50 °C, 6 h, **87a**: quantitative, **87b**: quantitative; (f) (i) Br₂, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, **TX63503**: 31%, **TX63505**: 27%.

Scheme 18(a):

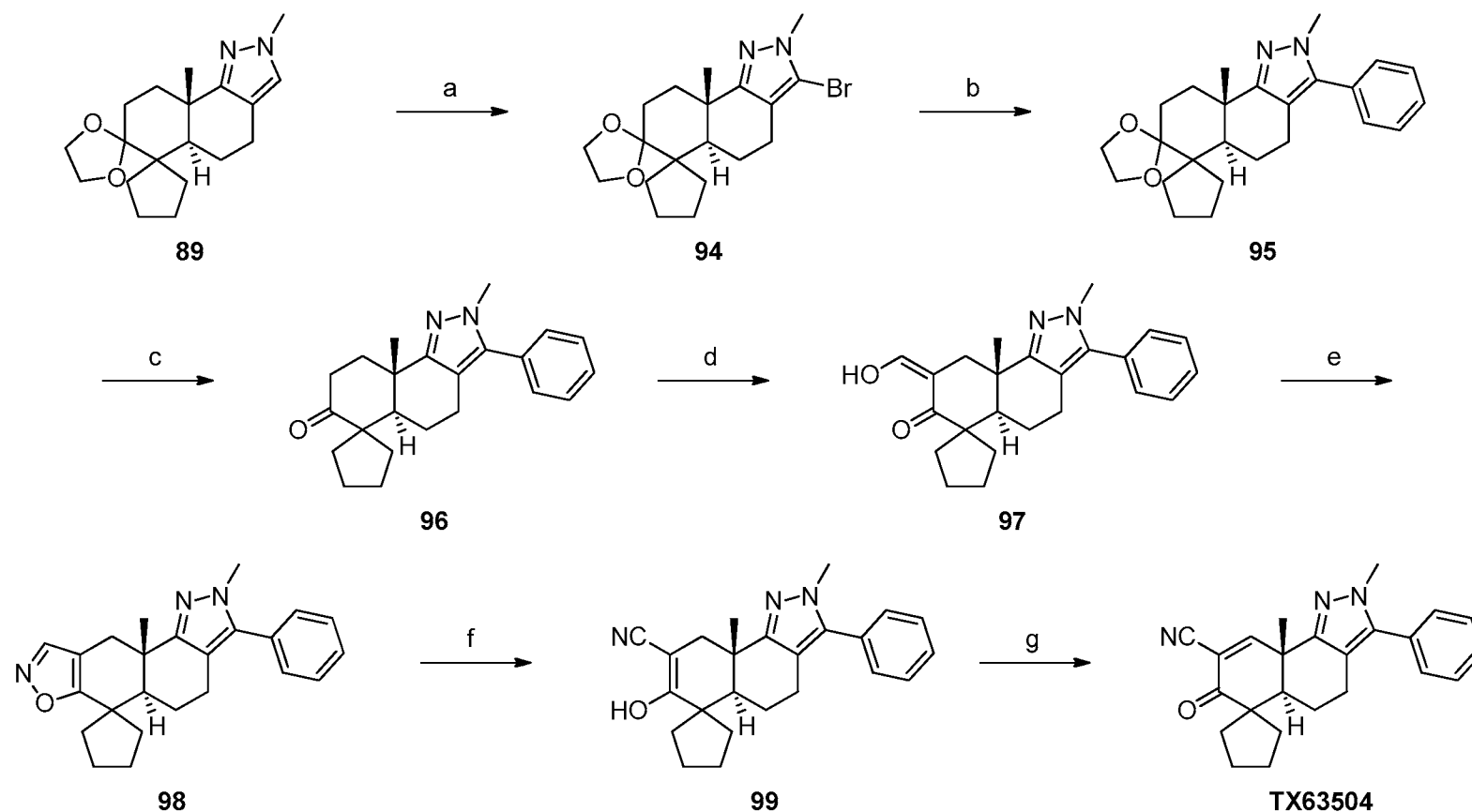


Scheme 18(b):



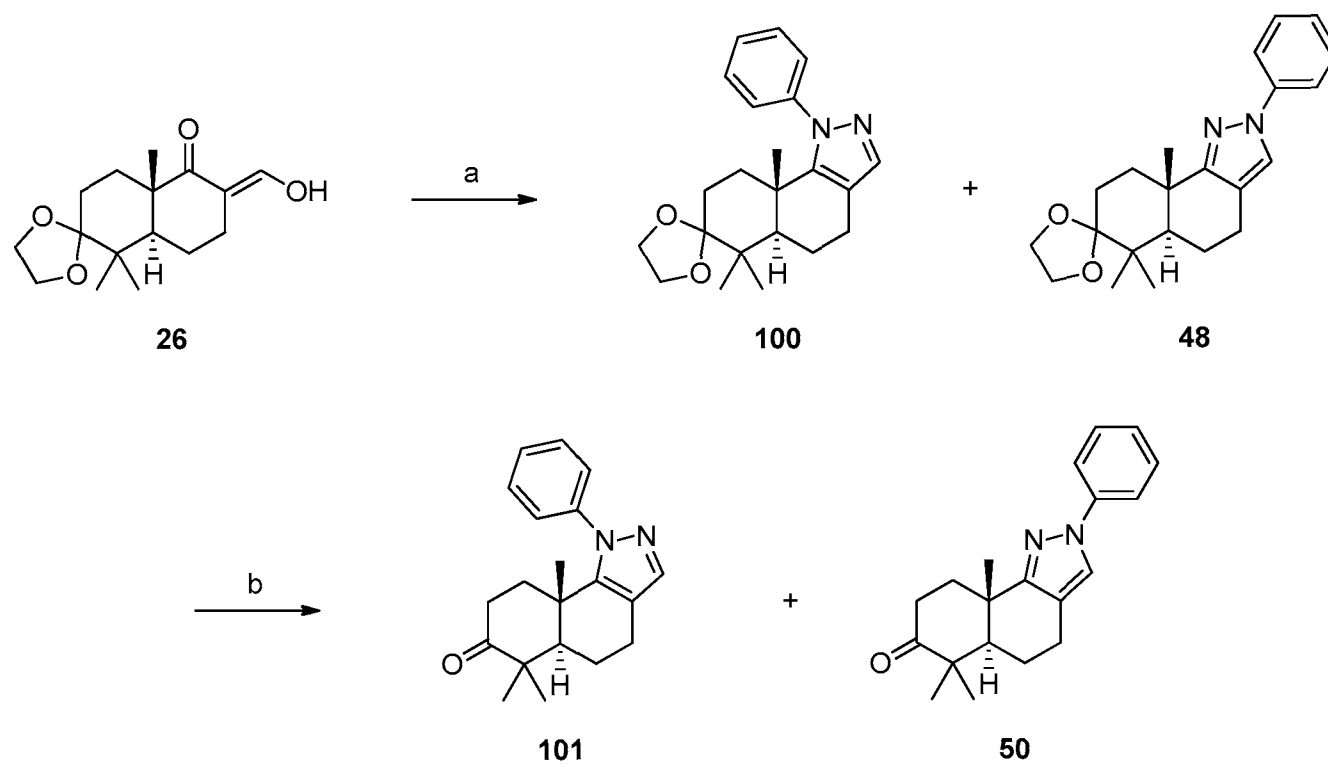
Reagents and conditions pertaining to Schemes 18(a) & (b): (a) $\text{KO}t\text{-Bu}$, $t\text{-BuOH}$, 1,4-dibromobutane, 45 °C, 78%; (b) H_2 , 20% $\text{Pd}(\text{OH})_2$, EtOH, 31%; (c) Ethylene glycol, $p\text{-TsOH}\cdot\text{H}_2\text{O}$, toluene, $-\text{H}_2\text{O}$, quantitative; (d) PDC, 45 °C, 73%; (e) HCO_2Et , NaOMe, RT, 12 h, 99%; (f) MeNHNH_2 , EtOH, RT $\rightarrow$ 60 °C, 75%; (g) 1 N HCl (aq), MeOH, RT, 12 h, quantitative; (h) HCO_2Et , NaOMe, RT, 12 h, quantitative; (i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, 50 °C, 12 h, 96%; (j) NaOMe, 50 °C, 6 h, quantitative; (k) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 38%.

Scheme 19:

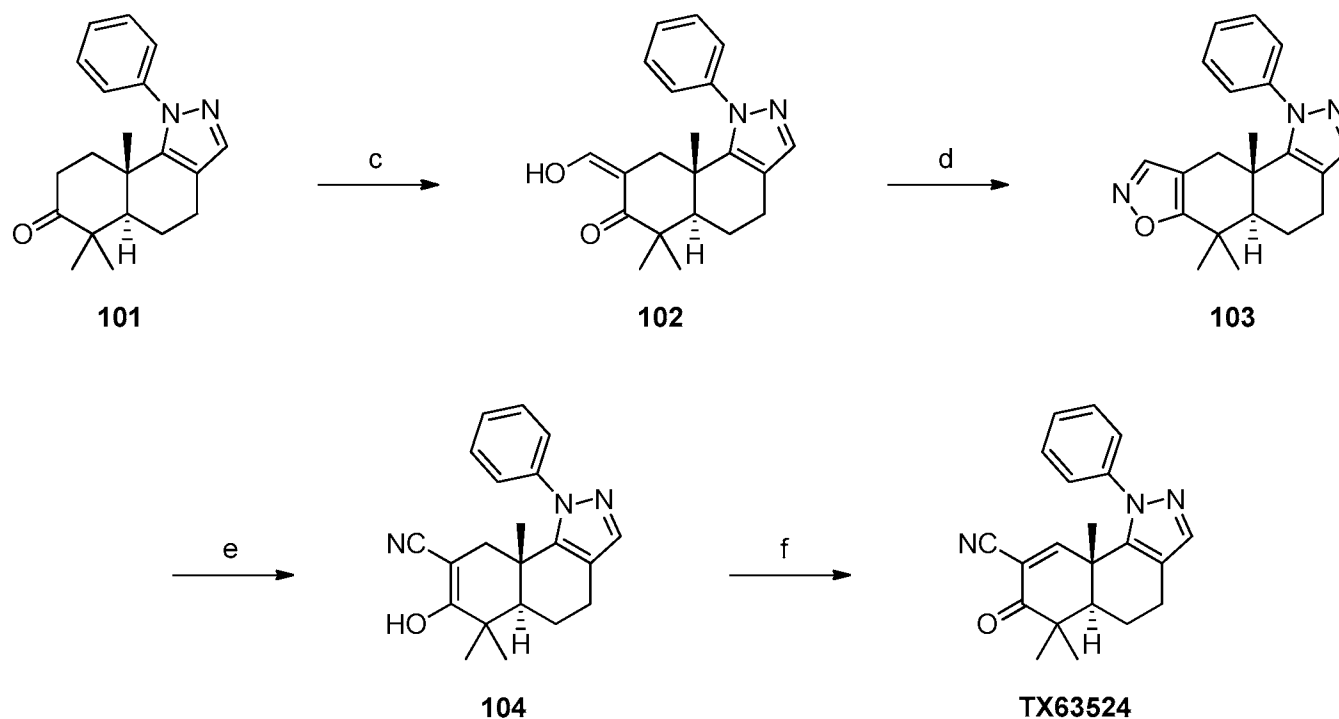


Reagents and conditions pertaining to Scheme 19: (a) 1,3-dibromo-5,5-dimethylhydantoin, CH_2Cl_2 , RT, 2 h, 62%; (b) phenylboronic acid, $\text{Pd}(\text{OAc})_2$, Ph_3P , K_3PO_4 , DME, 85 °C, 12 h, 73%; (c) 1 N HCl (aq), MeOH, RT, 12 h, quantitative; (d) HCO_2Et , NaOMe, RT, 12 h, 47%; (e) 5 $\text{NH}_2\text{OH}\cdot\text{HCl}$, 50 °C, 12 h, quantitative; (f) NaOMe, 50 °C, 6 h, quantitative; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C; (ii) pyridine, 50 °C, 12 h, 37%.

Scheme 20(a):

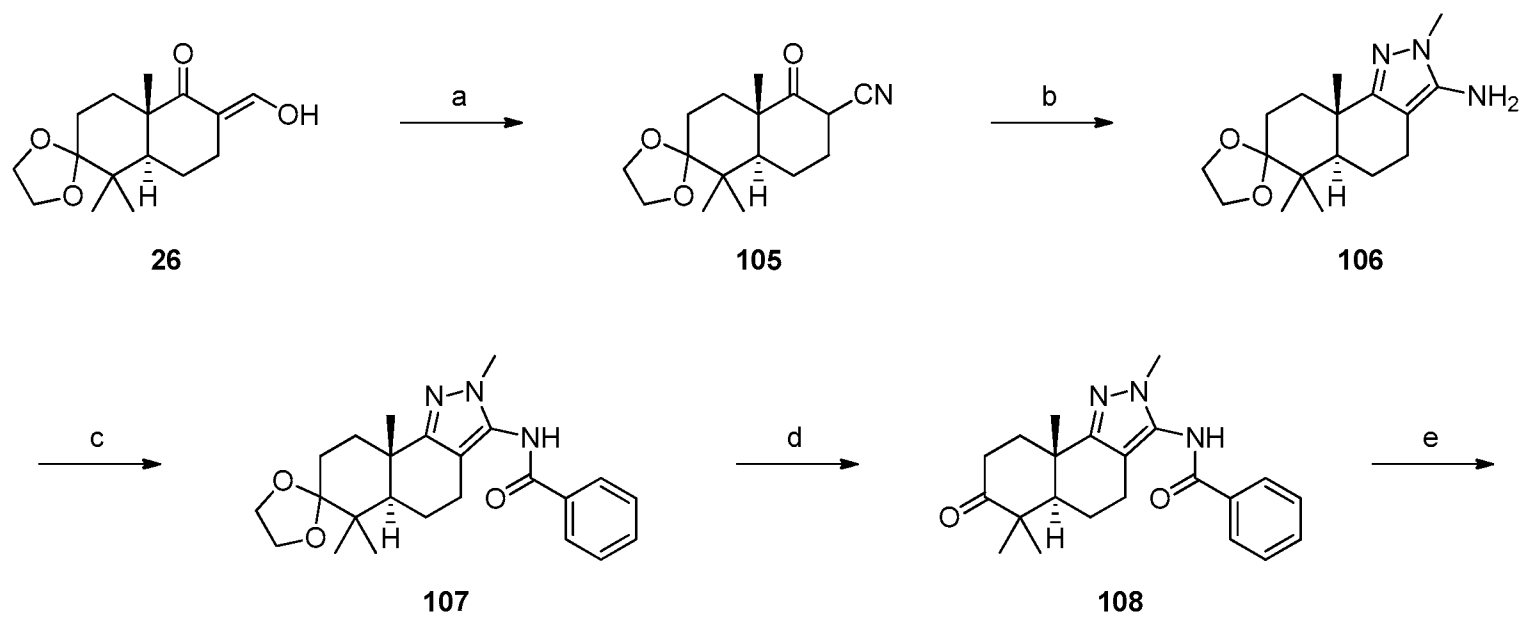


Scheme 20(b):

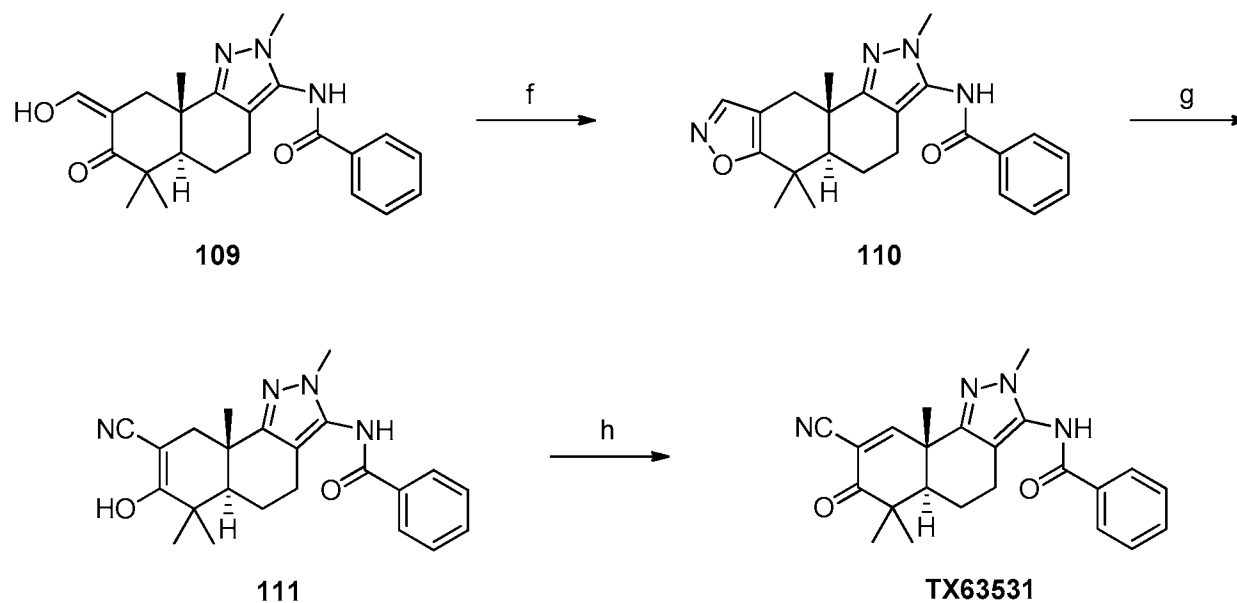


Reagents and conditions pertaining to Scheme 20: (a) (i) phenylhydrazine, toluene, 75 °C; (ii) TsOH·H₂O, toluene, 80 °C, 3 d; (b) 1 N HCl (aq),
 5 MeOH, RT, 12 h, **50**: 17%, **101**: 52%; (c) HCO₂Et, NaOMe, RT, 12 h, quantitative; (d) NH₂OH-HCl, 50 °C, 12 h, 89%; (e) NaOMe, 55 °C, 6 h,
 RT, 12 h, 89%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 30 min; (ii) pyridine, 50 °C, 12 h, 28%.

Scheme 21(a):

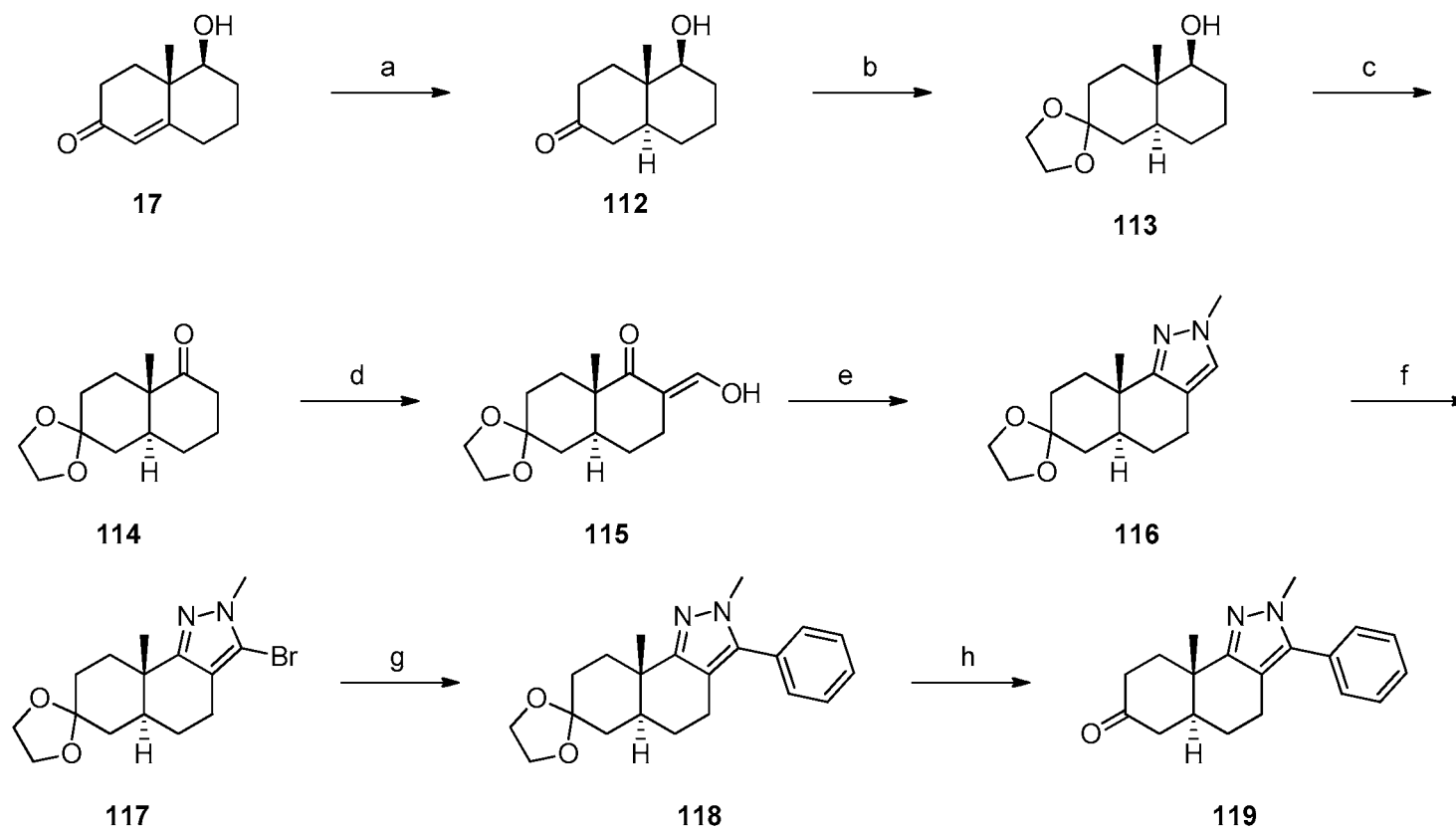


Scheme 21(b):

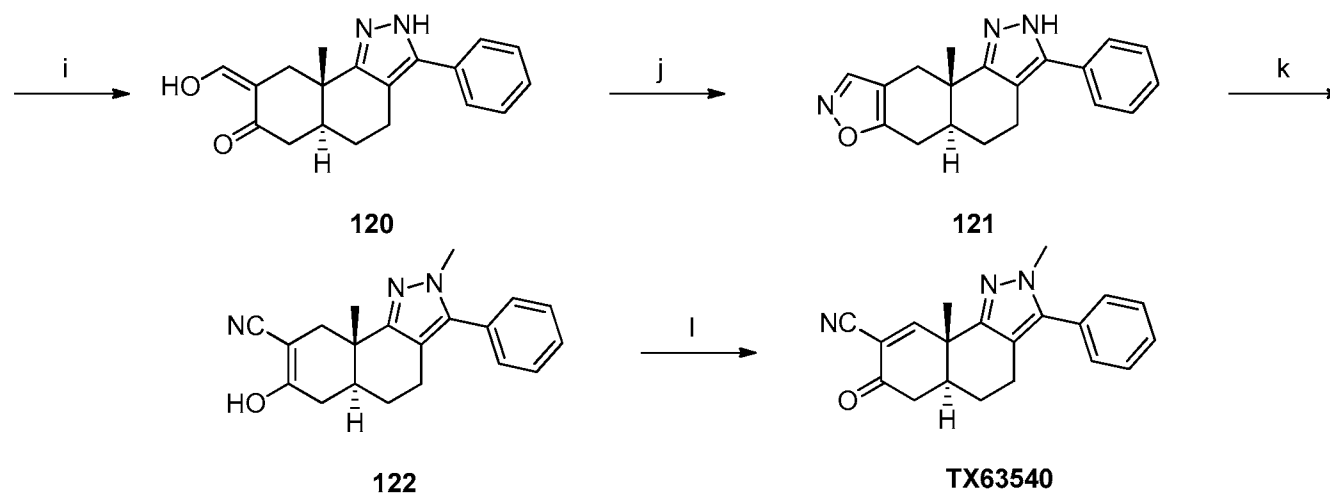


Reagents and conditions pertaining to Schemes 21(a) and (b): (a) (i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, TEA, EtOH, H_2O , RT, 16 h; (ii) NaOMe, MeOH, THF, RT;
 5 (b) MeNHNH_2 , EtOH, reflux, 16 hr; (c) PhCOCl , TEA, EtOAc; (d) 3 N HCl (aq), THF, RT; (e) HCO_2Et , NaOMe, RT, 16 hr; (f) $\text{NH}_2\text{OH}\cdot\text{HCl}$,
 50 °C, 12 h; (g) NaOMe, 50 °C, 6 h, (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h.

Scheme 22(a):

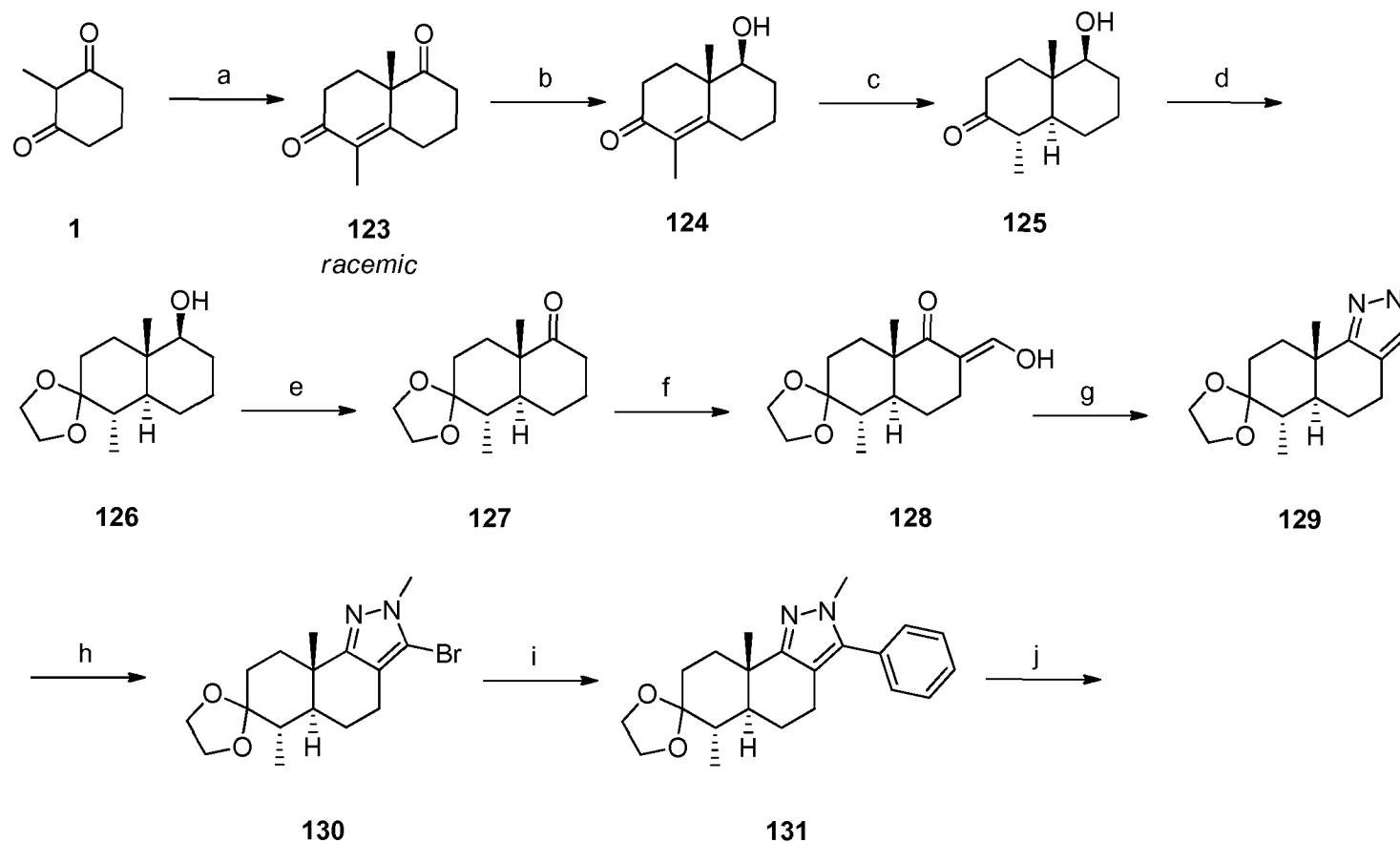


Scheme 22(b):

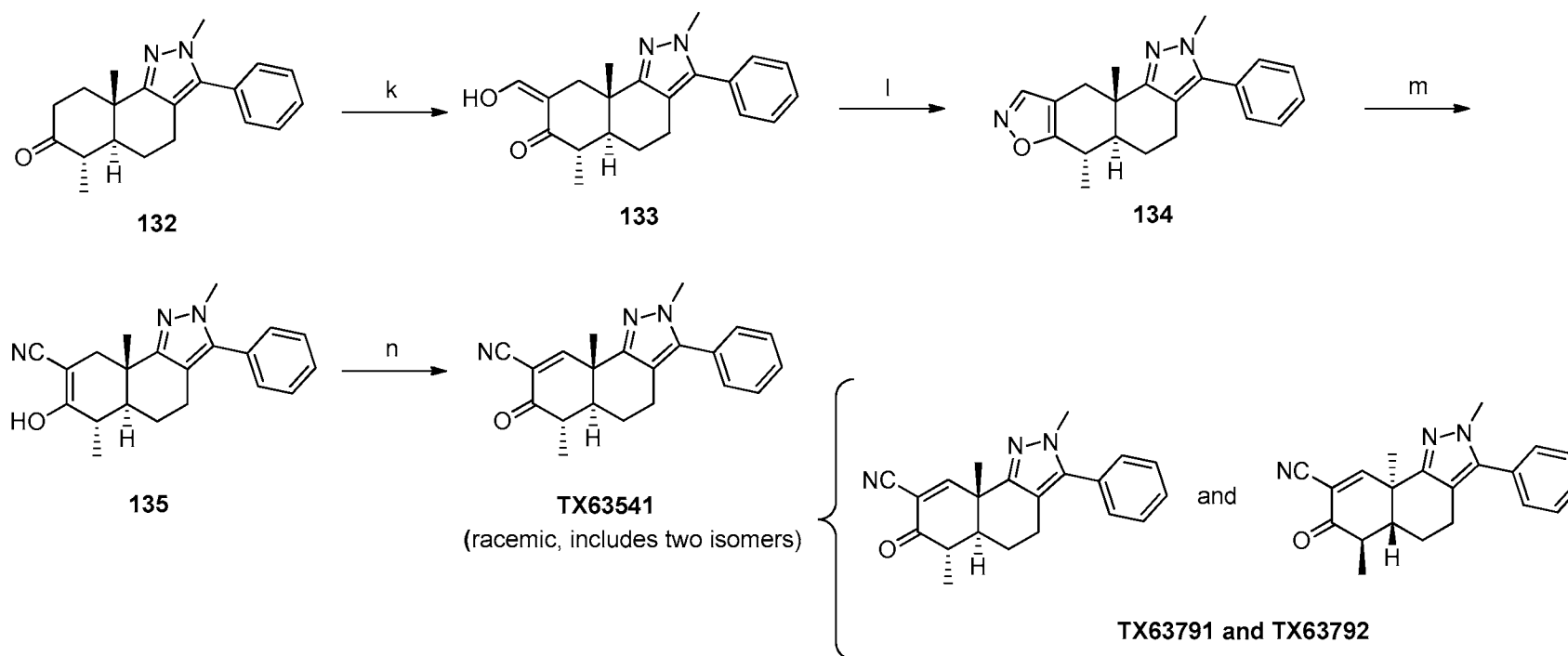


Reagents and conditions pertaining to Schemes 22 (a) & (b): (a) Li, NH₃, -78 °C, 45 min, 23%; (b) Ethylene glycol, *p*-TsOH•H₂O, benzene, H₂O, 75%; (c) PDC, MgSO₄, CH₂Cl₂, 2 d, RT, 90%; (d) HCO₂Et, NaOMe, RT, 12 h, 96%; (e) MeNHNH₂, EtOH, 60 °C, 2 h, 85%; (f) 1,3-dibromo-5,5-dimethylhydantoin, CH₂Cl₂, RT, 3 h, 64%; (g) phenylboronic acid, PPh₄, Pd(OAc)₂, K₃PO₄, DME, 85 °C, 16 h, 53%; (h) 3 N HCl (aq), MeOH, RT, 12 h, 91%; (i) HCO₂Et, NaOMe, RT, 12 h, 96%; (j) NH₂OH-HCl, 50 °C, 12 h, quantitative; (k) NaOMe, 50 °C, 6 h, quantitative; (l) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 28%.

Scheme 23(a):

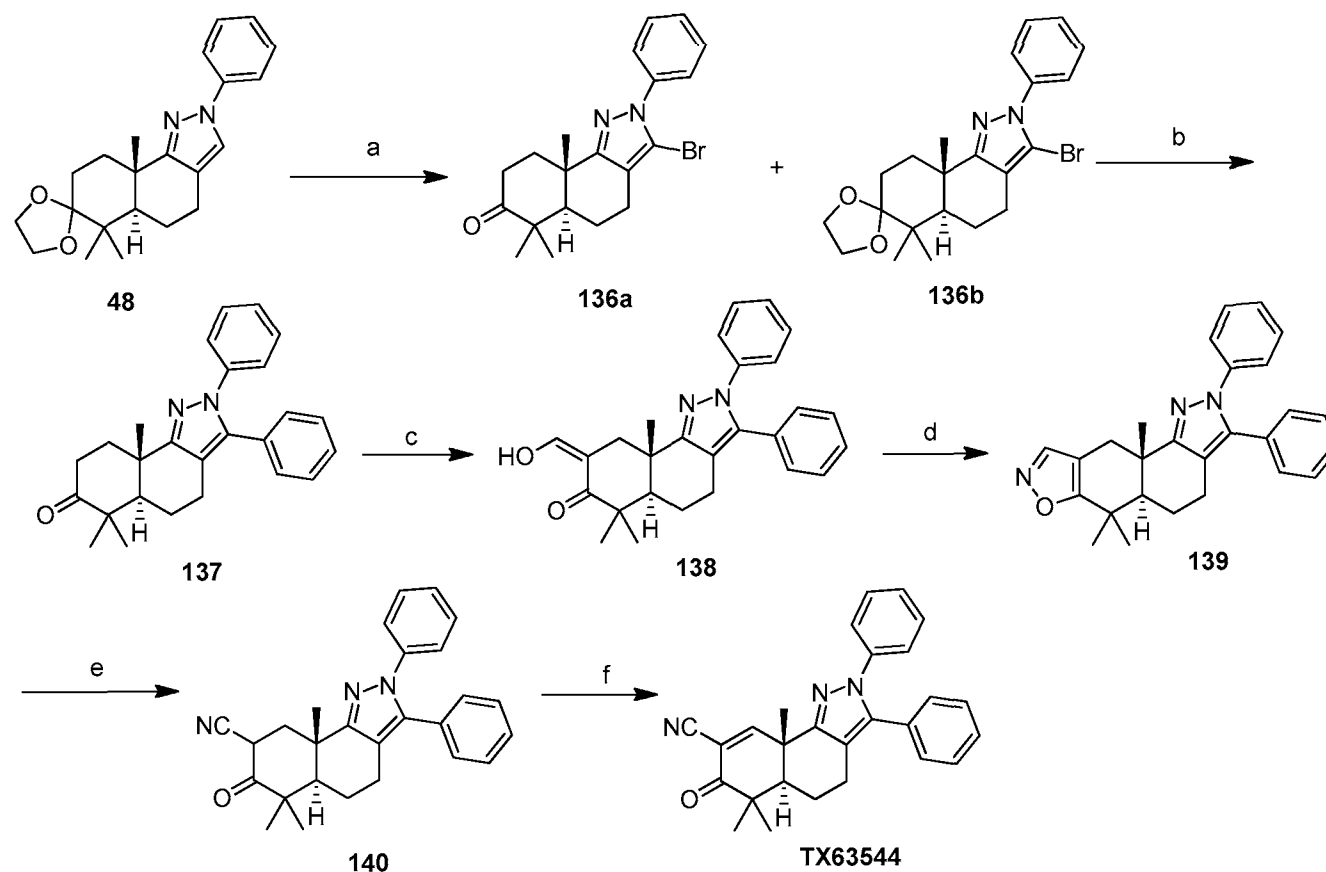


Scheme 23(b):



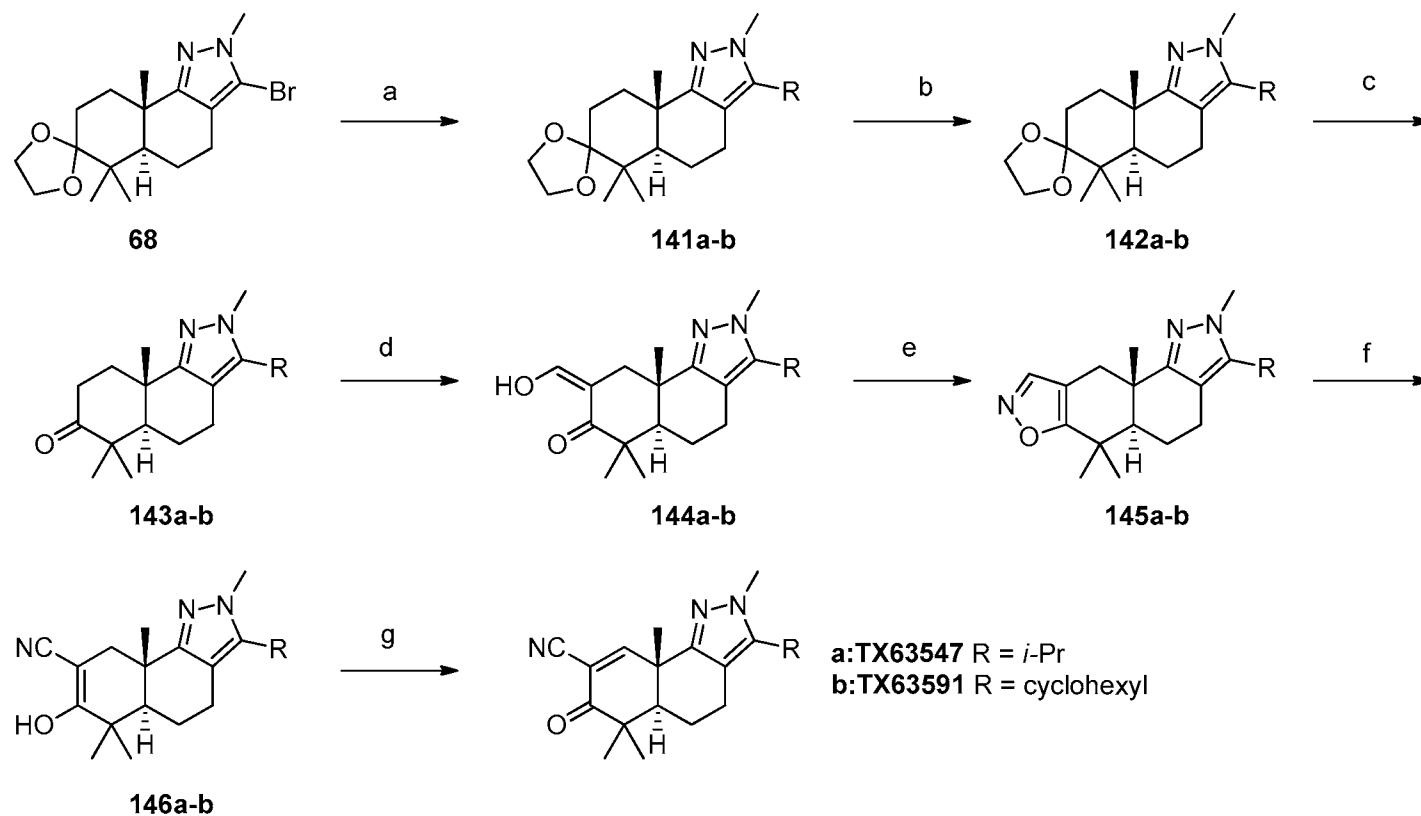
Reagents and conditions pertaining to Scheme 23(a) and (b): (a) (i) Ethyl vinyl ketone, Et₃N, MeCN, RT, 12 h; (ii) pyrrolidine, benzene, -H₂O, 48 h, 41%; (b) NaBH₄, EtOH, 0 °C, 45 min, 56%; (c) Li, NH₃, -78 °C, 45 min, 28%; (d) ethylene glycol, *p*-TsOH•H₂O, benzene, -H₂O, 62%; (e) 5 PDC, MgSO₄, CH₂Cl₂, 2 d, RT, 92%; (f) HCO₂Et, NaOMe, RT, 12 h, quantitative; (g) MeNHNH₂, EtOH, 60 °C, 2 h, 79%; (h) 1,3-dibromo-5,5-dimethylhydantoin, CH₂Cl₂, RT, 3 h, 74%; (i) phenylboronic acid, PPh₄, Pd(OAc)₂, K₃PO₄, DME, 85 °C, 16 h, 63%; (j) 3 N HCl (aq), MeOH, RT, 12 h, quantitative; (k) HCO₂Et, NaOMe, RT, 12 h, 95%; (l) NH₂OH-HCl, 50 °C, 12 h, quantitative; (m) NaOMe, 50 °C, 6 h, quantitative; (n) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 33%.

Scheme 24:



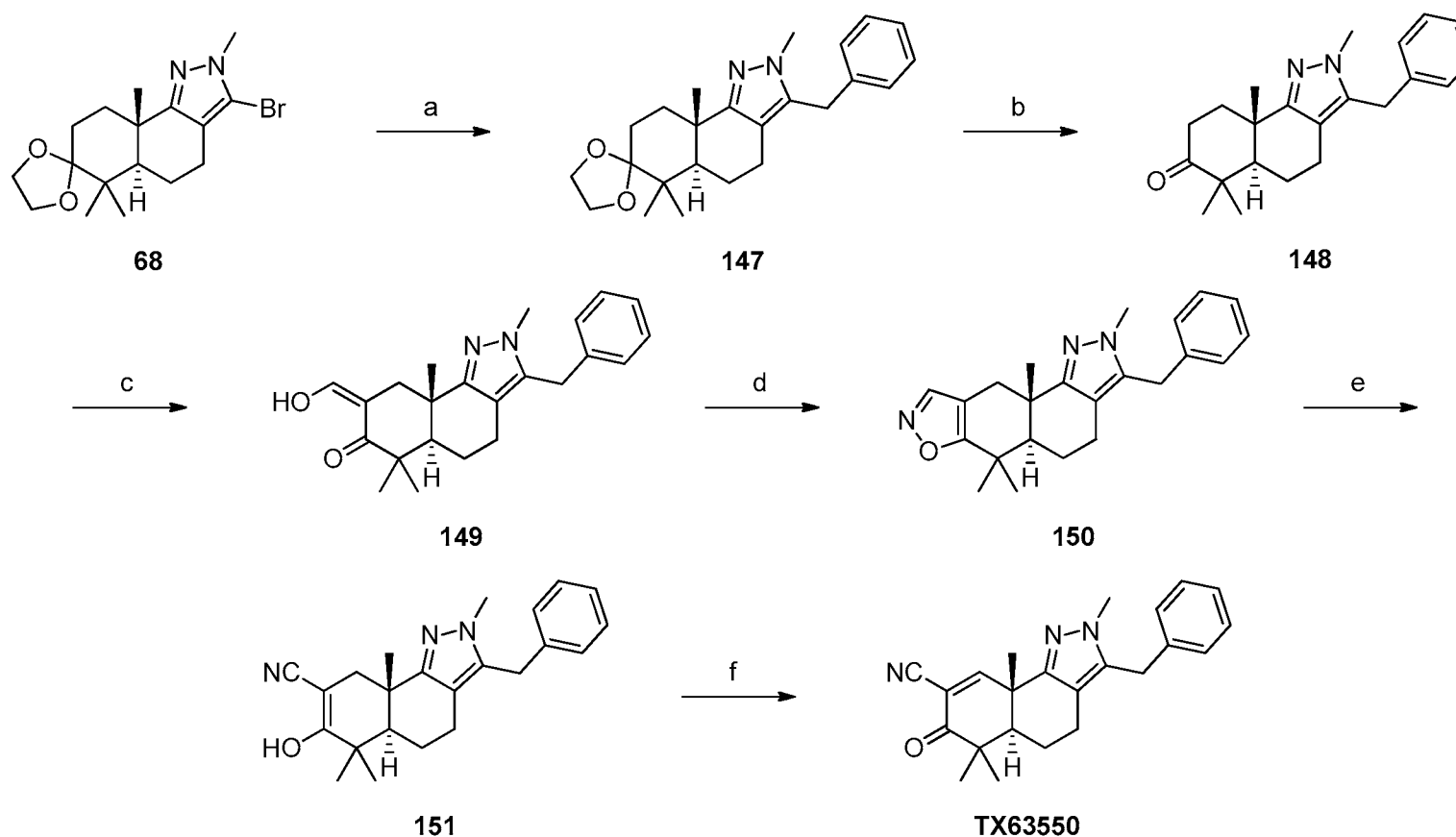
Reagents and conditions pertaining to Scheme 24: (a) 1,3-dibromo-5,5-dimethylhydantoin, CH_2Cl_2 , RT, 3 h; (b) (i) phenylboronic acid, $\text{Pd}(\text{OAc})_2$, Ph_3P , K_3PO_4 , DME, 85°C , 9 h; (ii) HCl (aq), MeOH; (c) HCO_2Et , NaOMe, RT, 12 h, quantitative; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, 50°C , 12 h, 94%;
 5 (e) NaOMe, 50°C , 6 h, 94%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C , 2 h; (ii) pyridine, 50°C , 12 h, 52%.

Scheme 25:



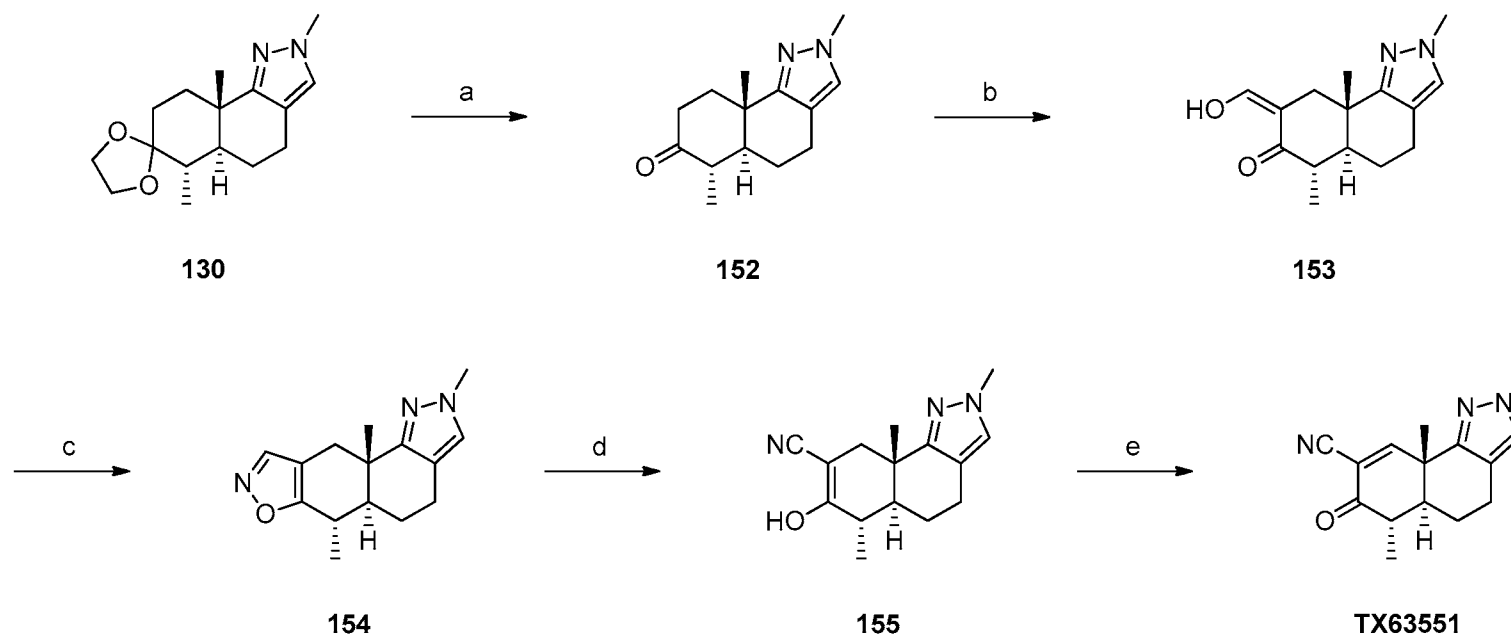
Reagents and conditions pertaining to Scheme 25: (a) isopropenyl pinacol boronate, Pd(II), 16 h, **141a**: 41%, **141b**: 40%; (b) H₂, 10% Pd/C, **142a**: 99%, **141b**: 93%; (c) 3 N HCl (aq), MeOH, RT, 12 h, **142a**: 99%, **141b**: 93%; (d) HCO₂Et, NaOMe, RT, 12 h, **144a**: quantitative, **144b**: quantitative; (e) NH₂OH-HCl, 50 °C, 12 h, **145a**: quantitative, **145b**: 87%; (f) NaOMe, 50 °C, 6 h, **146a**: 99% **141b**: 97%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, **TX63547**: 15% **TX63591**: 13%.

Scheme 26:



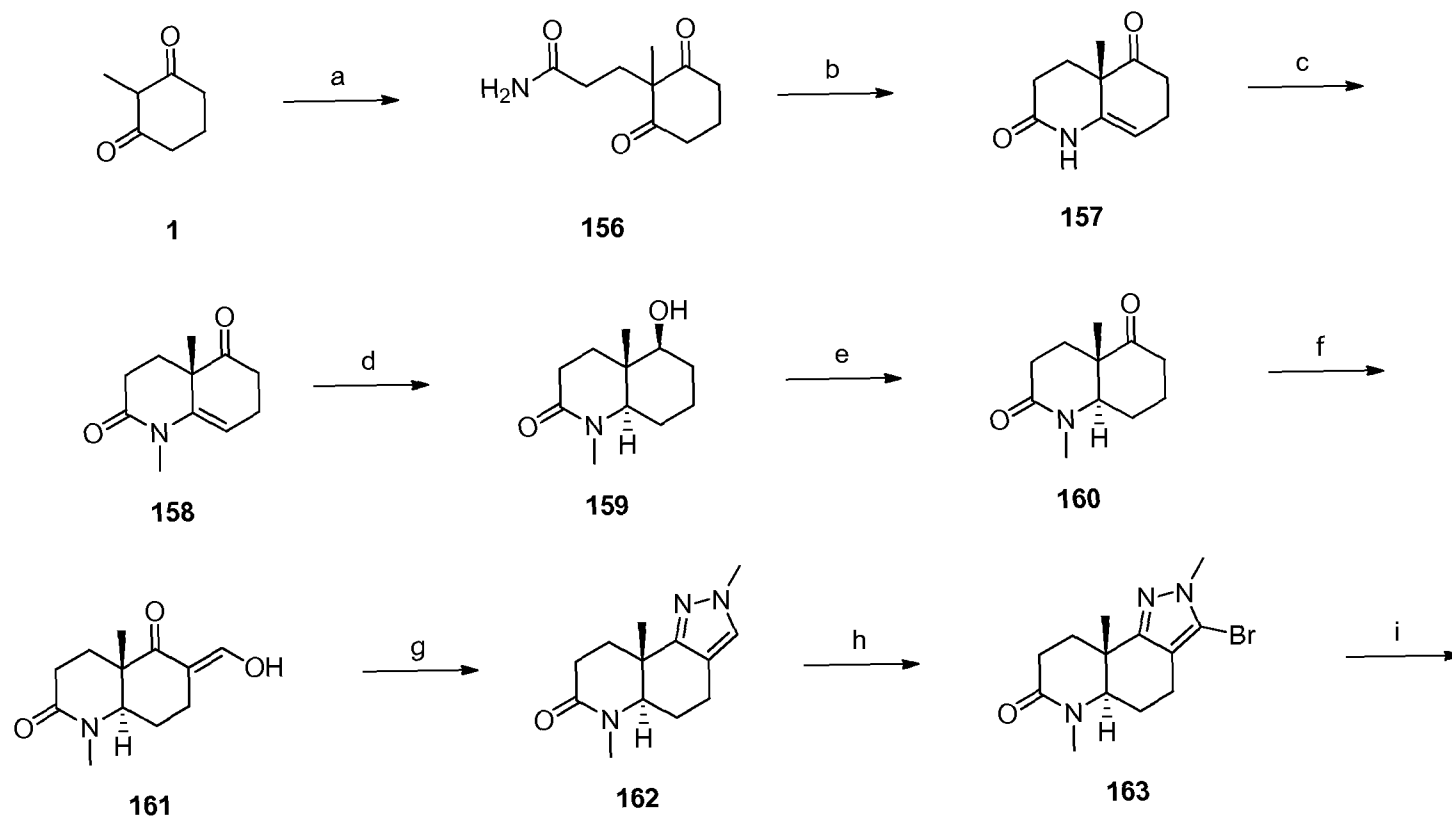
Reagents and conditions pertaining to Scheme 26: (a) benzylboronic acid pinacol ester, Pd(dppf)Cl₂, K₂CO₃, dioxane, 100 °C, 16 h, 47%; (b) 1 N HCl (aq), MeOH, rt, 16 h, 90%; (c) HCO₂Et, NaOMe, RT, 12 h, quantitative; (d) NH₂OH-HCl, 50 °C, 12 h, 97%; (e) NaOMe, 50 °C, 6 h, 32%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 36%.

Scheme 27:

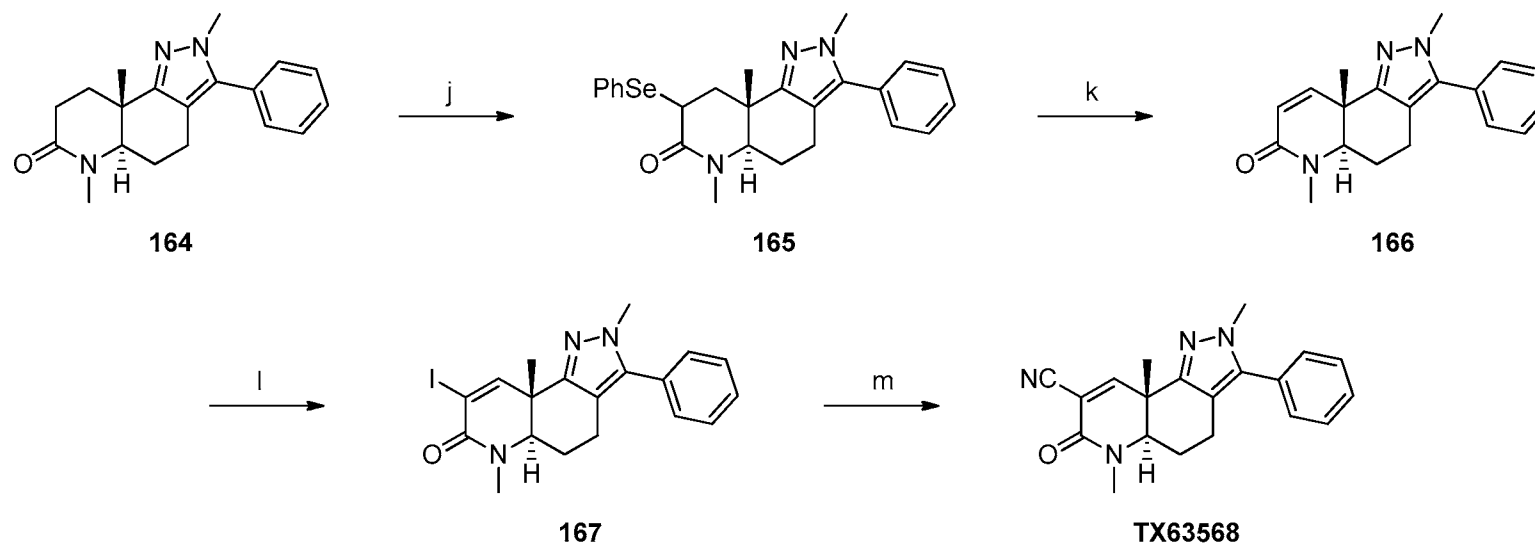


Reagents and conditions pertaining to Scheme 27: (a) 3 N HCl (aq), MeOH, RT, 12 h, quantitative; (b) HCO₂Et, NaOMe, RT, 12 h, 99%; (c) 5 NH₂OH-HCl, 50 °C, 12 h, 98%; (d) NaOMe, 50 °C, 6 h, quantitative; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 38%.

Scheme 28(a):

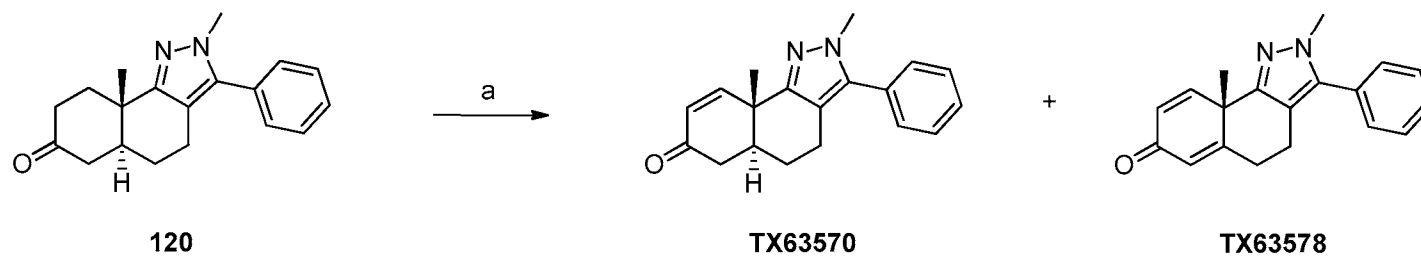


Scheme 28(b):



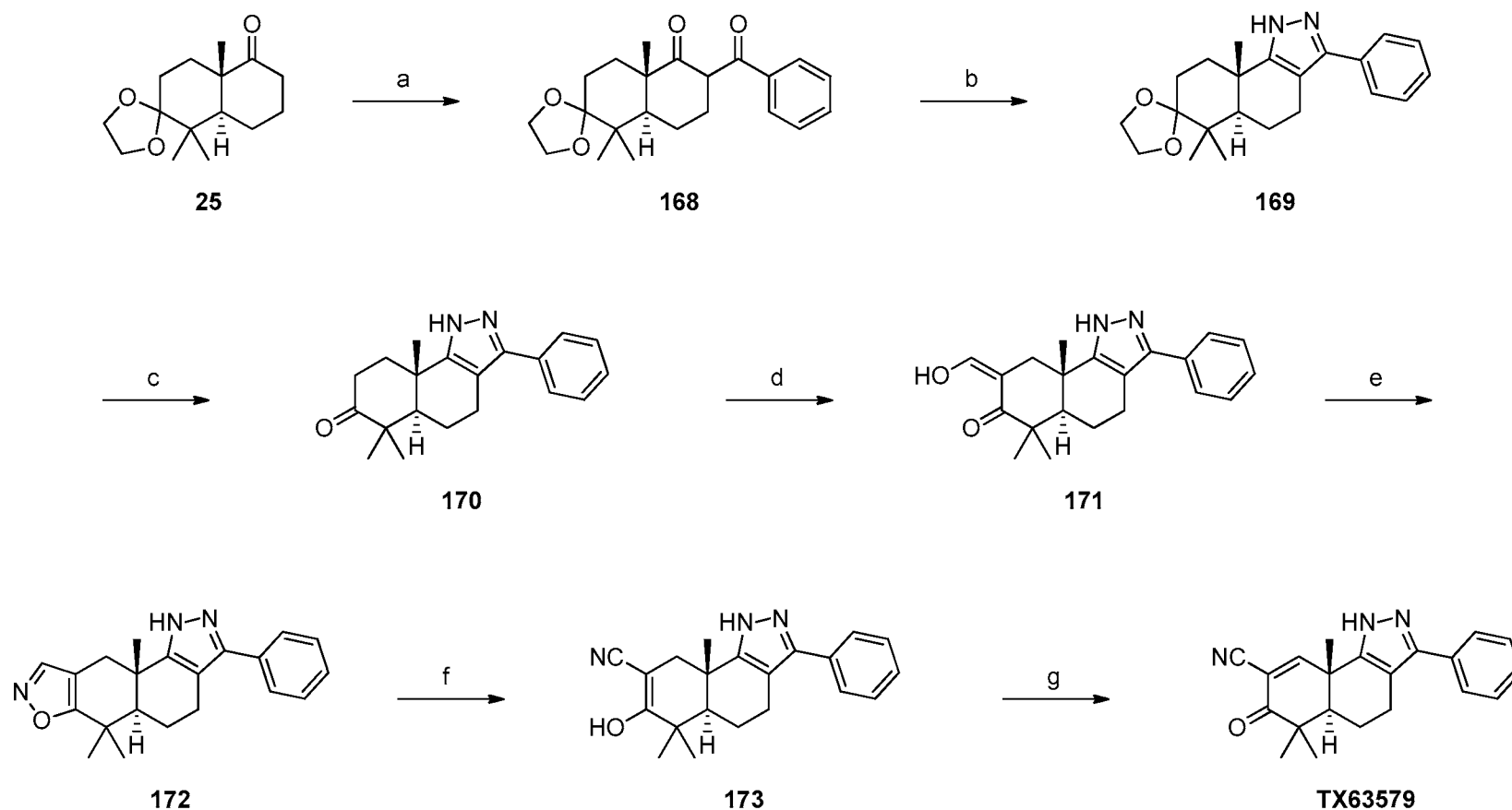
Reagents and conditions pertaining to Schemes 28(a) & (b): (a) Acrylamide, Et₃N, 85 °C, 16 h, 96% ; (b) AcOH, 160 °C (microwave), 1 h, 73%;
 5 (c) NaH, MeI, DMF, THF, 0 °C to rt, 2 h, 68%; (d) H₂, PtO₂, AcOH, H₂O, rt, 16 h; (e) TPAP, NMO, 4 Å molecular sieves, CH₂Cl₂, rt, 1 h, 79%
 2 steps; (f) HCO₂Et, NaOMe, 0 °C to rt, 3 h; (g) MeNHNH₂, EtOH, 60 °C, 3 h, 93% 2 steps; (h) 1,3-dibromo-5,5-dimethylhydantoin, CH₂Cl₂, rt,
 5 h, 49%; (i) phenylboronic acid, Pd(OAc)₂, Ph₃P, K₃PO₄, DME, 110 °C (microwave), 2.5 h, 95%; (j) (i) LDA, THF, -78 °C, 30 min; (ii)
 PhSeCl, -78 °C, 1 h, 45%; (k) H₂O₂, EtOAc, THF, rt, 30 min, 90%; (l) I₂, pyridine, CCl₄, rt to 65 °C, 41 h, 60%; (m) Zn(CN)₂, Pd(Ph₃P)₄, DMF,
 80 °C, 20 min, 89%.

Scheme 29:



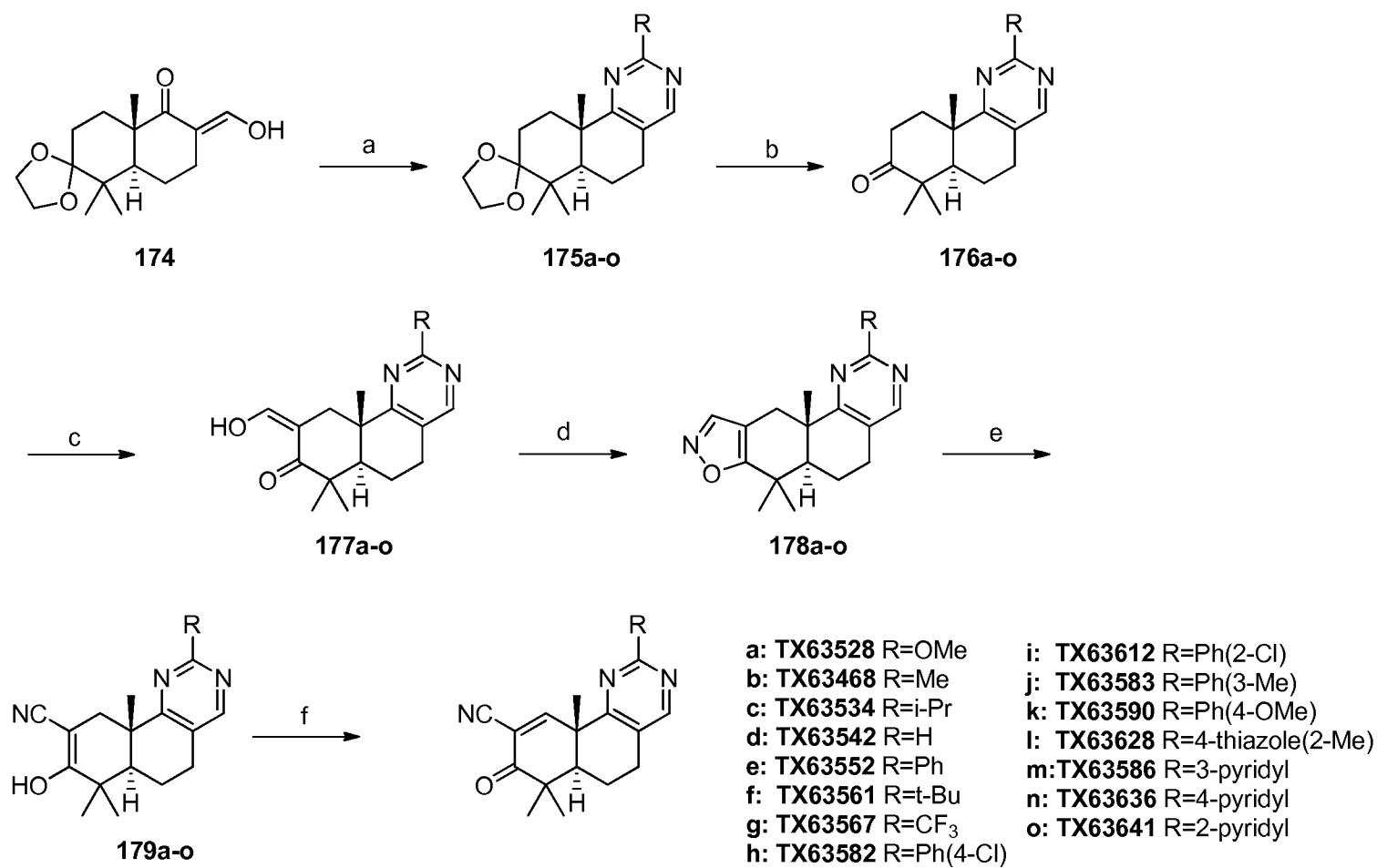
Reagents and conditions pertaining to Scheme 29: (a) IBX.

Scheme 30:



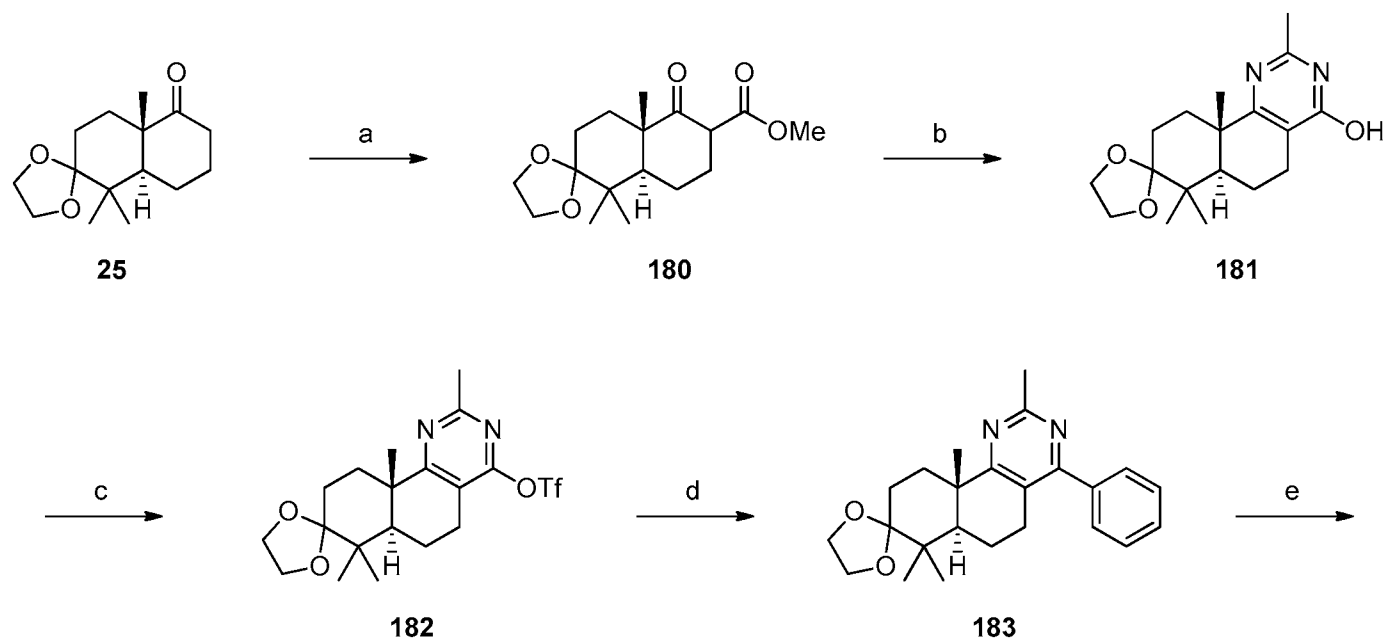
Reagents and conditions pertaining to Scheme 30: (a) PhCOCl , $i\text{Pr}_2\text{Net}$, MgBr_2 , CH_2Cl_2 , rt, 16 h; (b) NH_2NH_2 , EtOH , 63°C , 1 h, 38% 2 steps; (c) 1 N HCl (aq), MeOH , rt, 16 h, quantitative; (d) HCO_2Et , NaOMe , RT, 12 h, 84%; (e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, 50°C , 12 h, 84%; (f) NaOMe , 50°C , 6 h, quantitative; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF , 0°C , 2 h; (ii) pyridine, 50°C , 12 h, 28%.

Scheme 31:

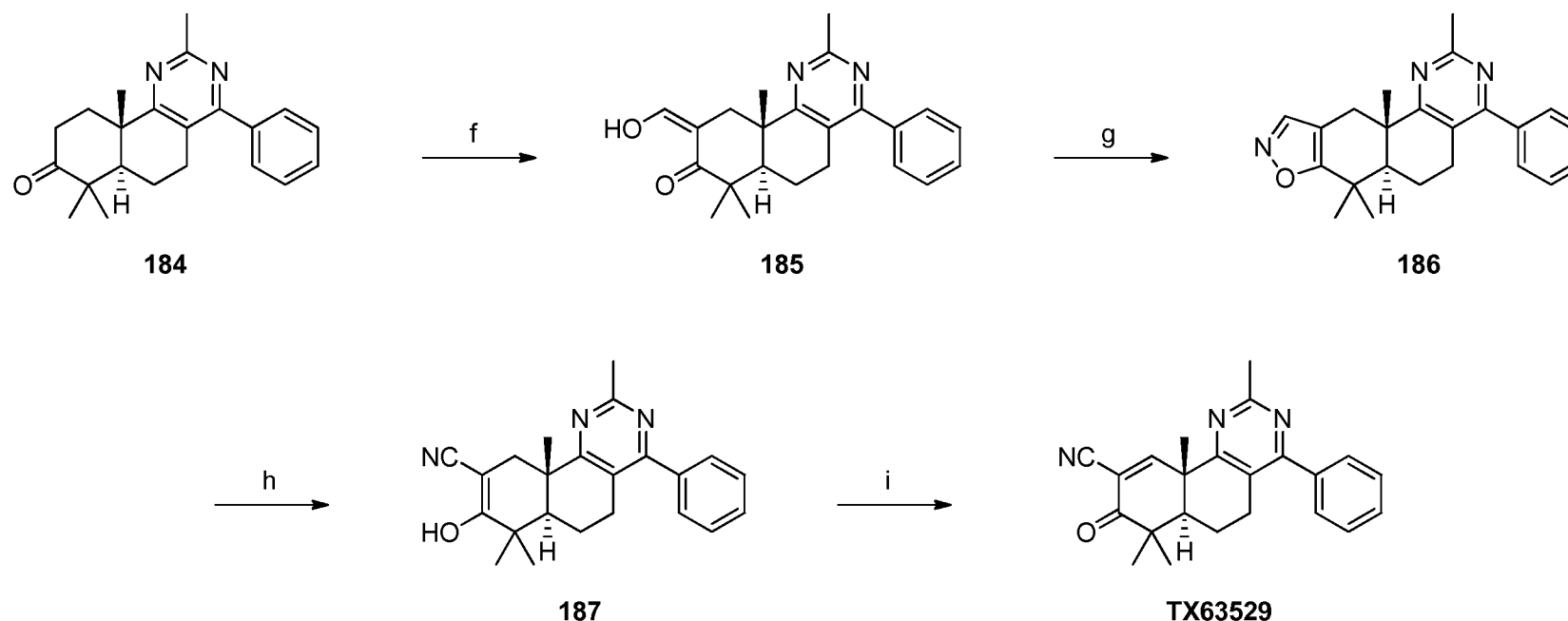


Reagents and conditions pertaining to Schemes 31: (a) substituted amidine, piperidine, *i*PrOH, 85°C, sealed tube, 2 d; (b) 3 N HCl (aq); (b) HCO₂Et, NaOMe, RT, 16 h; (c) NH₂OH-HCl, 50 °C, 16 h; (d) NaOMe, 50 °C, 6 h; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 16 h.

Scheme 32(a):

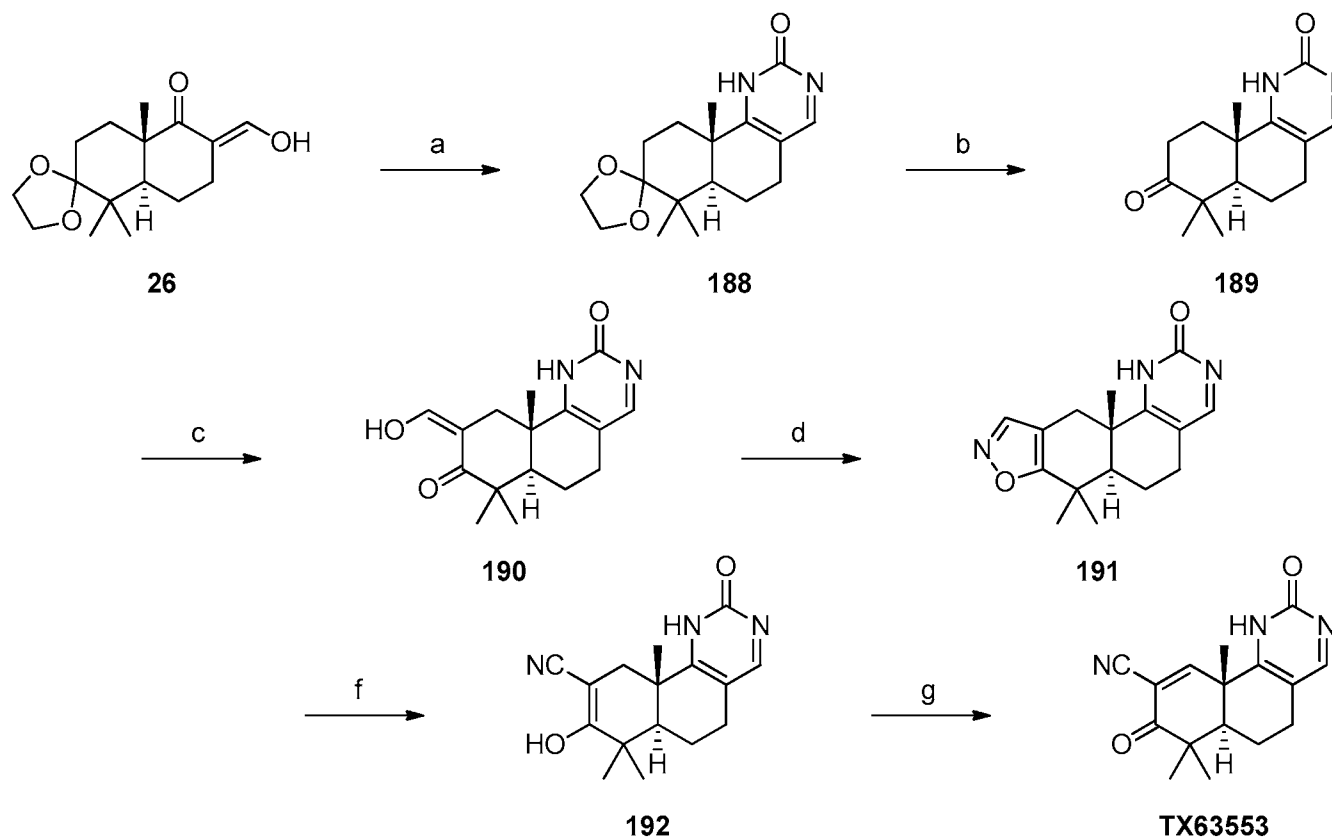


Scheme 32(b):



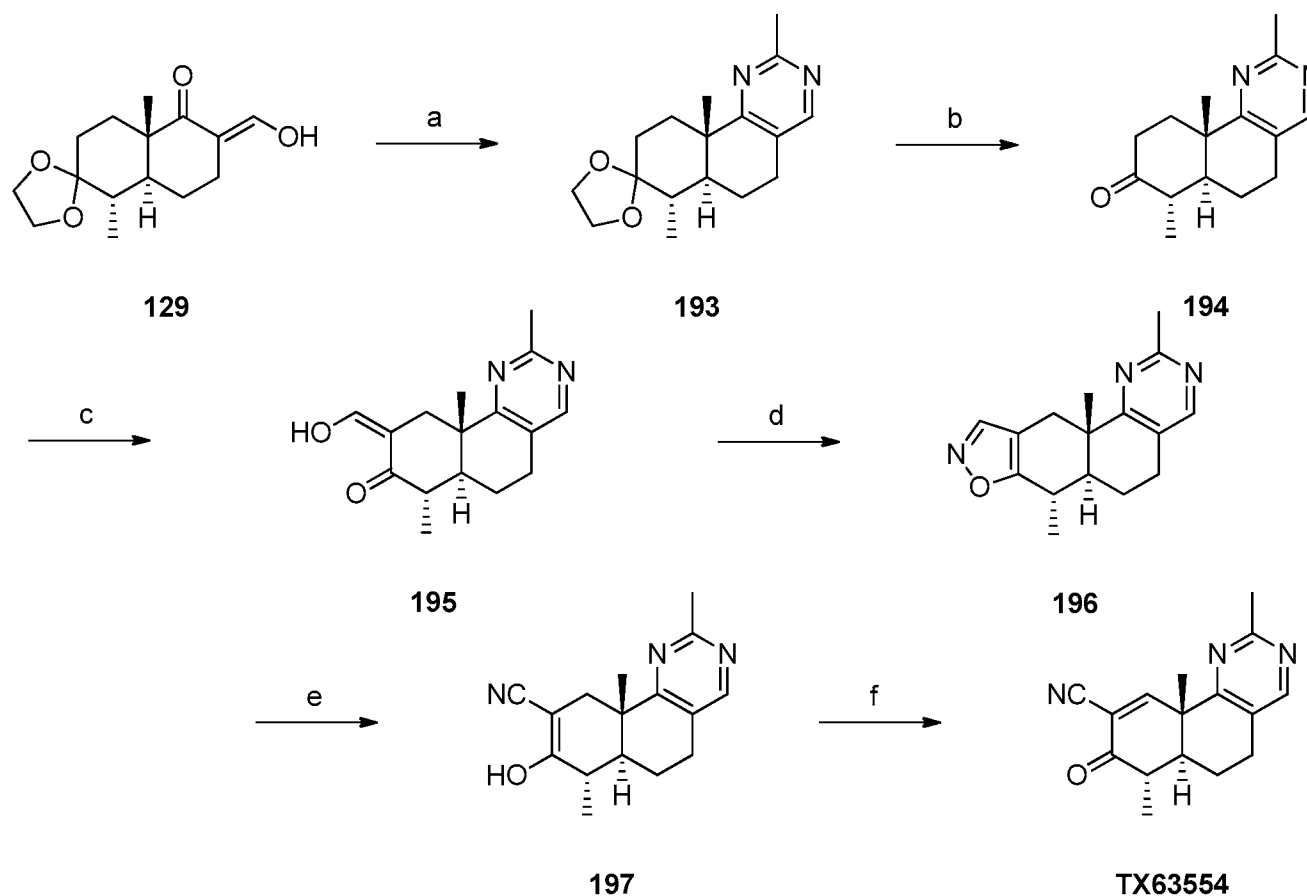
Reagents and conditions pertaining to Scheme 32: (a) $(\text{MeO})_2\text{CO}$, NaH, THF, reflux, 3 h, 87%; (b) acetamidine-HCl, piperidine, *i*-PrOH, reflux, 2 d, 62%; (c) TiF_2O , Et_3N , CHCl_3 , 0 °C, 2 h, 83%; (d) phenylboronic acid, PPh_4 , $\text{Pd}(\text{OAc})_2$, K_3PO_4 , DME, 85 °C, 16 h, 83%; (e) 3 N HCl (aq), MeOH, RT, 12 h, quantitative; (f) HCO_2Et , NaOMe, RT, 12 h, quantitative; (g) $\text{NH}_2\text{OH}\cdot\text{HCl}$, 50 °C, 12 h, quantitative; (h) NaOMe, 50 °C, 6 h, quantitative; (i) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 67%.

Scheme 33:



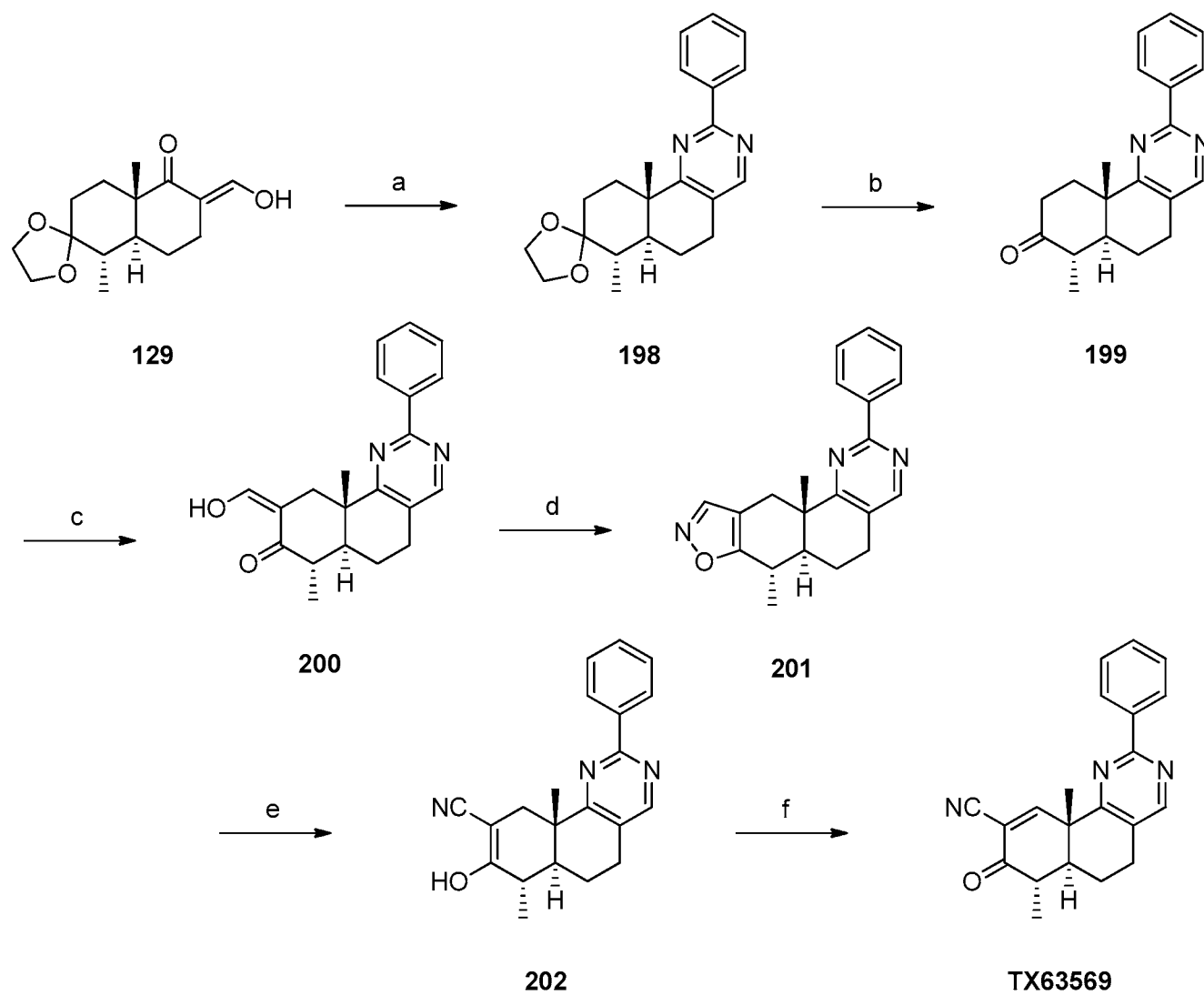
Reagents and conditions pertaining to Scheme 33: (a) (i) urea, dioxane, reflux, 3 d; (ii) MeOH, NaOMe, reflux, 3 d; (b) 1 N HCl (aq), MeOH, RT, 12 h, 71% 2 steps; (c) HCO₂Et, NaOMe, RT to 50 °C, 49%; (c) NH₂OH-HCl, 50 °C, 12 h; (d) NaOMe, 50 °C, 6 h, 15% 2 steps; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 2 h; (ii) pyridine, 50 °C, 12 h, 31%.

Scheme 34:



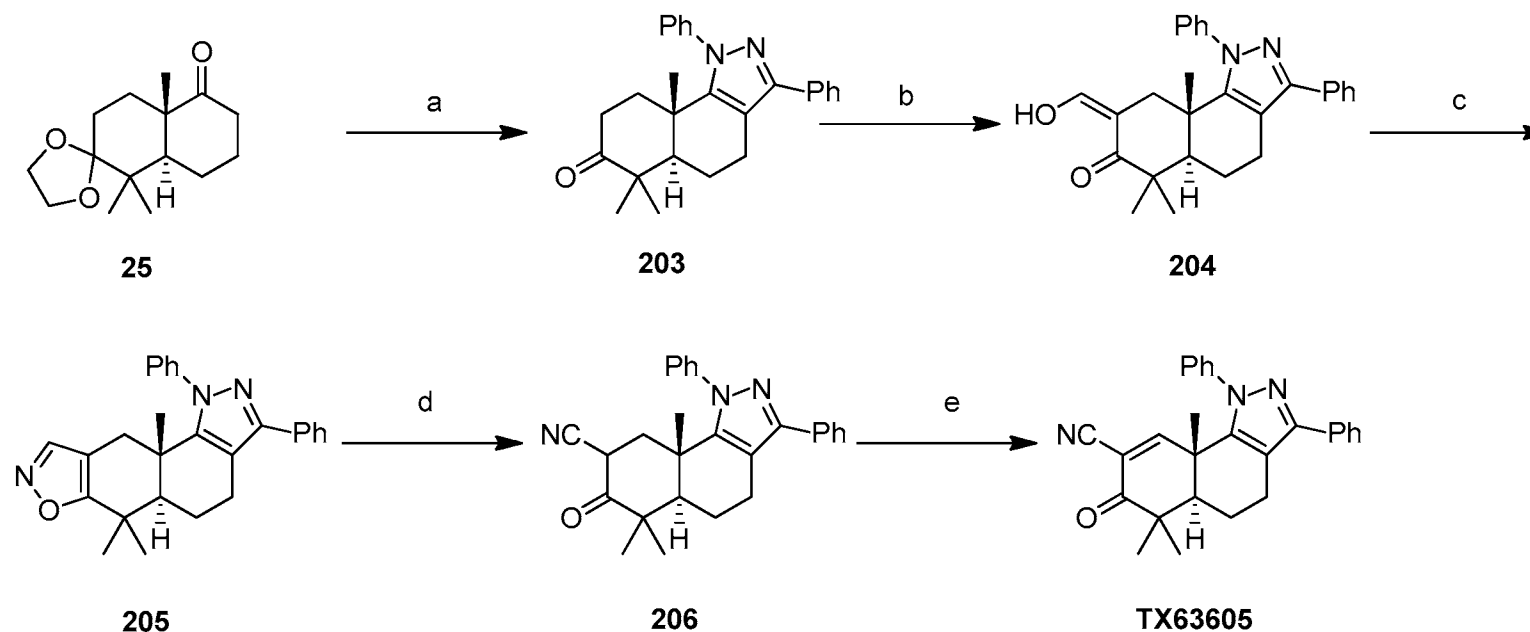
Reagents and conditions pertaining to Scheme 35: (a) acetamidine-HCl, piperidine, *i*-PrOH, reflux, 2 d, 48%; (b) 3 N HCl (aq), MeOH, RT, 16 h, 94%; (c) HCO₂Et, NaOMe, RT, 16 h, 90%; (d) NH₂OH-HCl, 50 °C, 16 h, 98%; (e) NaOMe, RT, 48 h, 80%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 h, 51%.

Scheme 35:



Reagents and conditions pertaining to Schemes 35: (a) acetamidine-HCl, piperidine, *i*-PrOH, 85 °C, 4 d, 60%; (b) 3 N HCl (aq), MeOH, RT, 16 h, 95%; (c) HCO₂Et, NaOMe, RT, 16 h, 91%; (d) NH₂OH-HCl, 50 °C, 16 h, 89%; (e) NaOMe, RT, 16 h, quantitative; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 h, 36%.

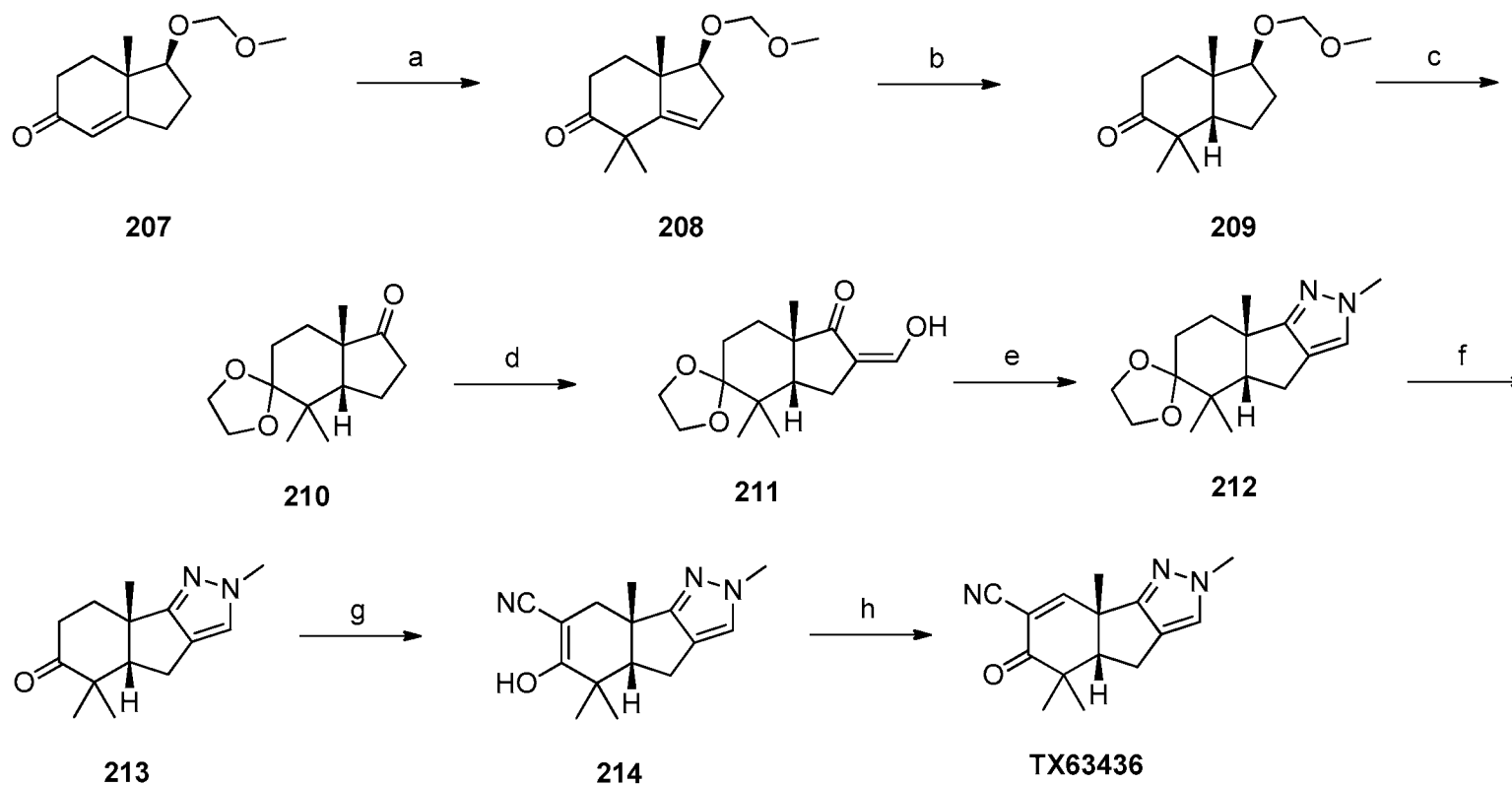
Scheme 36:



5

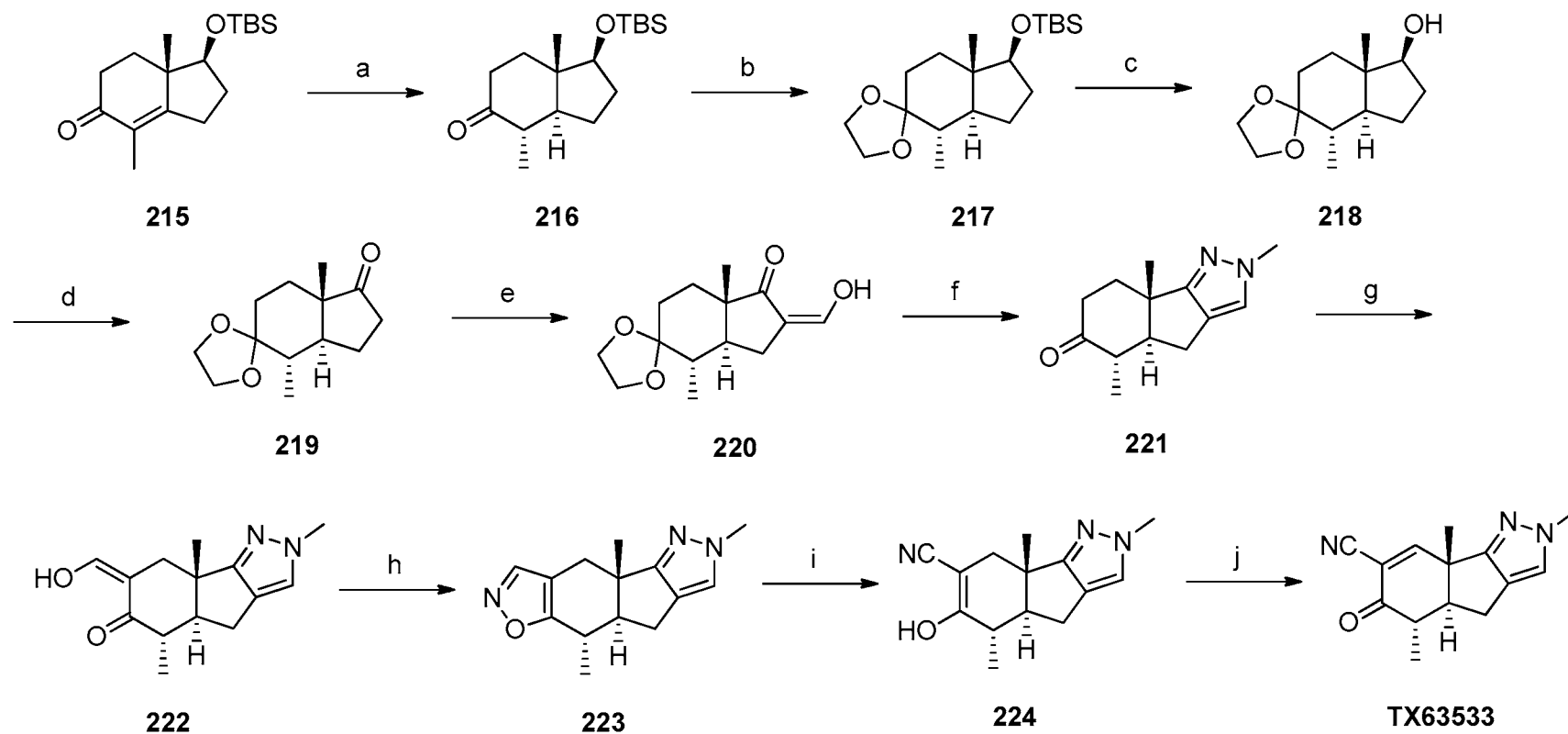
Reagents and conditions pertaining to Schemes 36: (a) (i) BzCl, MgBr₂-Et₂O, DIPEA, DCM, 16 hr; (ii) PhNHNH₂, EtOH, 80°C, 16 hr; (b) HCO₂Et, NaOMe, RT, 16 h; (c) NH₂OH-HCl, 50 °C, 16 h; (d) NaOMe, MeOH, THF, RT, 16 h; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 h, 36%.

Scheme 37:



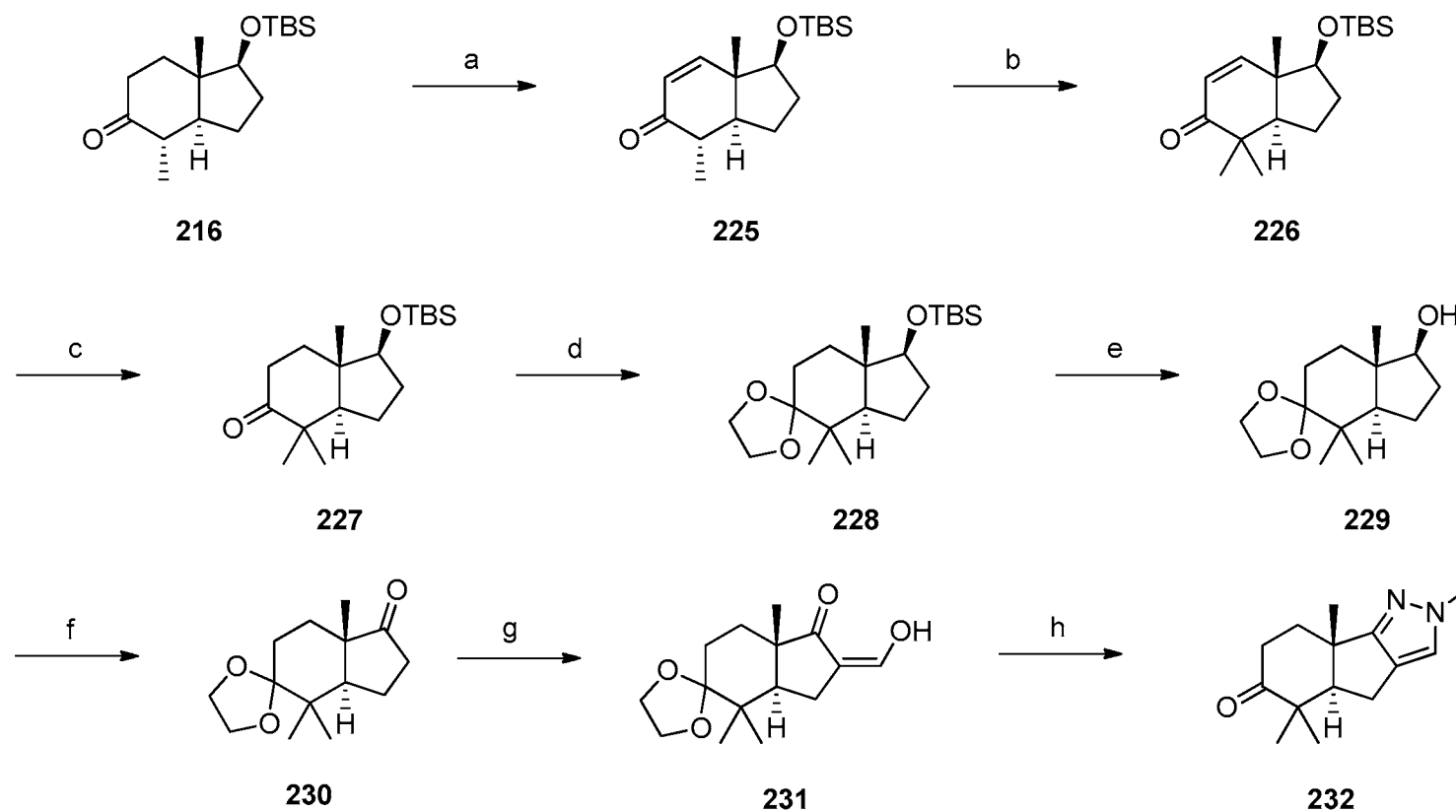
Reagents and conditions pertaining to Schemes 37(a) & (b): (a) KO t -Bu, t -BuOH, MeI, 55%; (b) H₂, 10% Pd/C, EtOAc, 12 h, 99%; (c) (i) ethylene glycol, p -TsOH $\cdot$ H₂O, toluene, -H₂O; (ii) PDC, CH₂Cl₂, RT, 22 h, 73%; (d) HCO₂Et, NaOMe, 0 °C to RT, 1 h, quantitative; (e) MeNHNH₂, EtOH, 65 °C, 4 h, 27%; (f) 1 N HCl(aq), THF, RT, 24 h, 90%; (g) (i) LDA, THF, -78 °C, 30 min; (ii) TsCN, -78 °C, 30 min, 80%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 12 h, 46%.

Scheme 38:

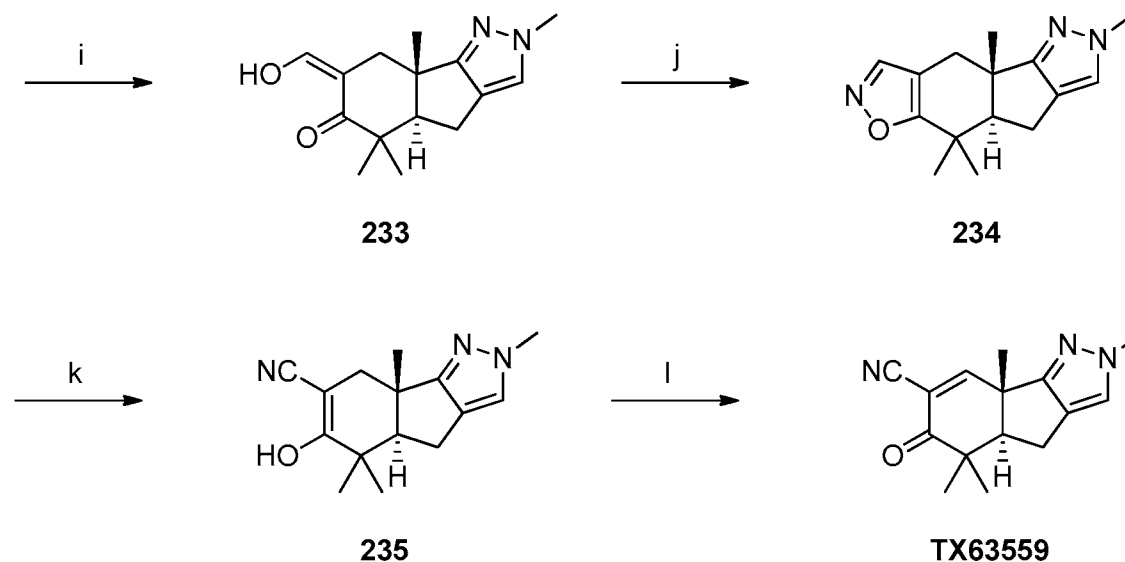


Reagents and conditions pertaining to Schemes 38: (i) H_2 , 10% Pd/C, THF, 0 °C to RT, 4 d; (ii) NaOMe, MeOH, RT, 12 h, 42%; (b) ethylene glycol, *p*-TsOH•H₂O, toluene, H₂O, 100%; (c) TBAF•H₂O, THF, RT, 3 d, 94%; (d) PDC, CH₂Cl₂, RT, 12 h, 100%; (e) HCO₂Et, NaOMe, 0 °C to RT, 2 h, 100%; (f) (i) MeNHNH₂, EtOH, 65 °C, 12 h, 83%; (ii) 1 N HCl(aq), THF, RT, 3 d, 83%; (g) HCO₂Et, NaOMe, 0 °C to RT, 2 h, 100%; (h) NH₂OH-HCl, 60 °C, 12 h, 100%; (i) NaOMe, 50 °C, 6 h, 100%; (j) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to r.t, 2 h; (ii) pyridine, 60 °C, 2 h, 20%.

Scheme 39(a):

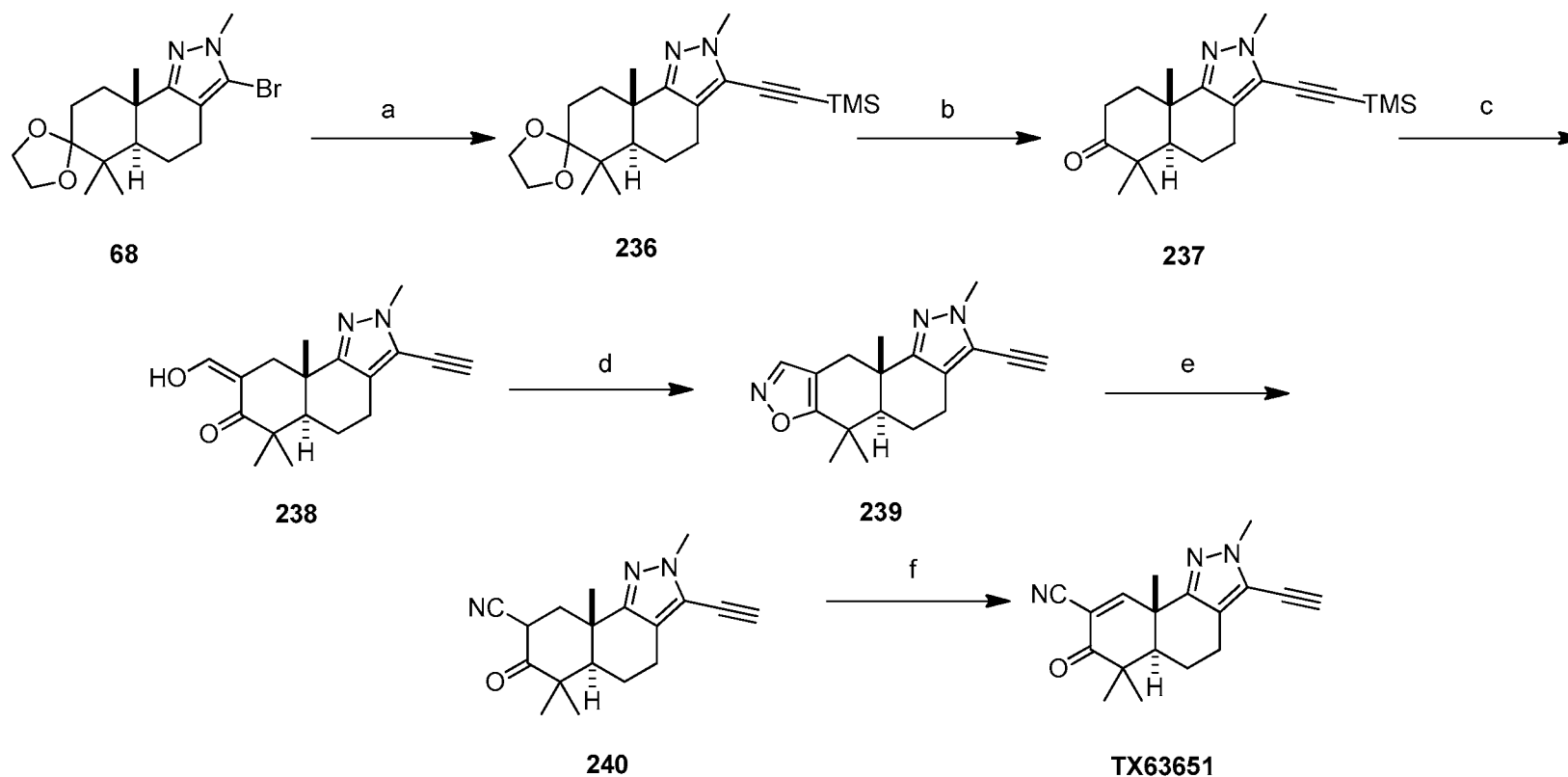


Scheme 39(b):



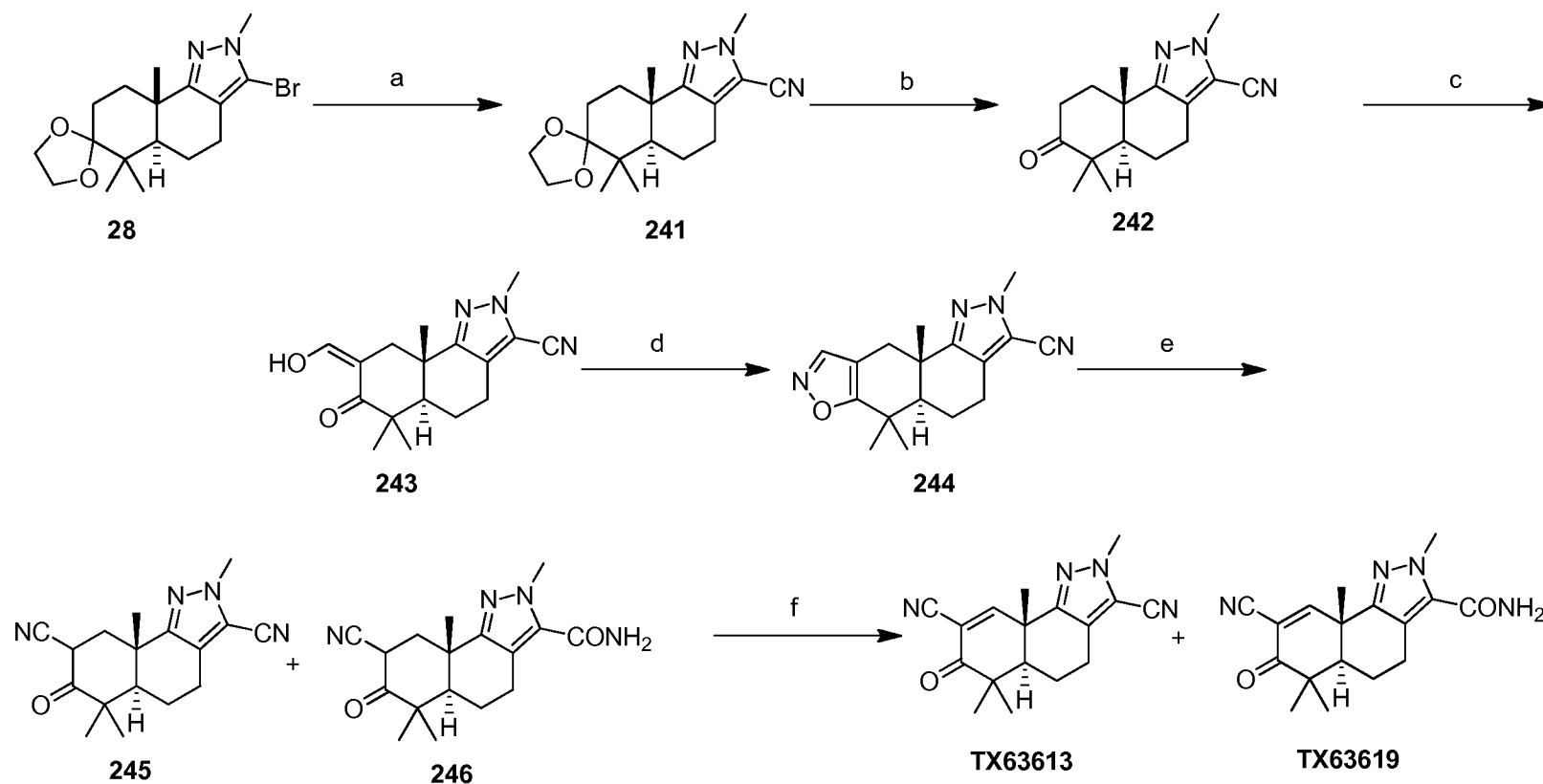
Reagents and conditions pertaining to Schemes 39(a) & (b): (a) (i) hexamethyldisilazane, NaI, TMSCl, MeCN, RT, 12 h; (ii) Pd(OAc)₂, MeCN, RT, 12 h, 79%; (b) (i) KHMDS, THF, 0 °C, 30 min; (ii) MeI, 0 °C, 30 min, 81%; (c) H₂, 10% Pd/C, THF, RT, 3 h, 99%; (d) methylethyldioxolane, ethylene glycol, *p*-TsOH, CH₂Cl₂, RT, 2 d, 99%; (e) TBAF, THF, RT, 4 d, 89%; (f) PDC, CH₂Cl₂, RT, 12 h, 90%; (g) HCO₂Et, NaOMe, 0 °C to RT, 2 h, quantitative; (h) (i) MeNHNH₂, EtOH, 65 °C, 12 h; (ii) 1 N HCl(aq), THF, RT, 2 d, 76%; (i) HCO₂Et, NaOMe, 0 °C to RT, 2 h, 96%; (j) NH₂OH-HCl, 60 °C, 12 h, 91%; (k) NaOMe, 50 °C, 6 h, 71%; (l) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 5 h, 71%.

Scheme 40:



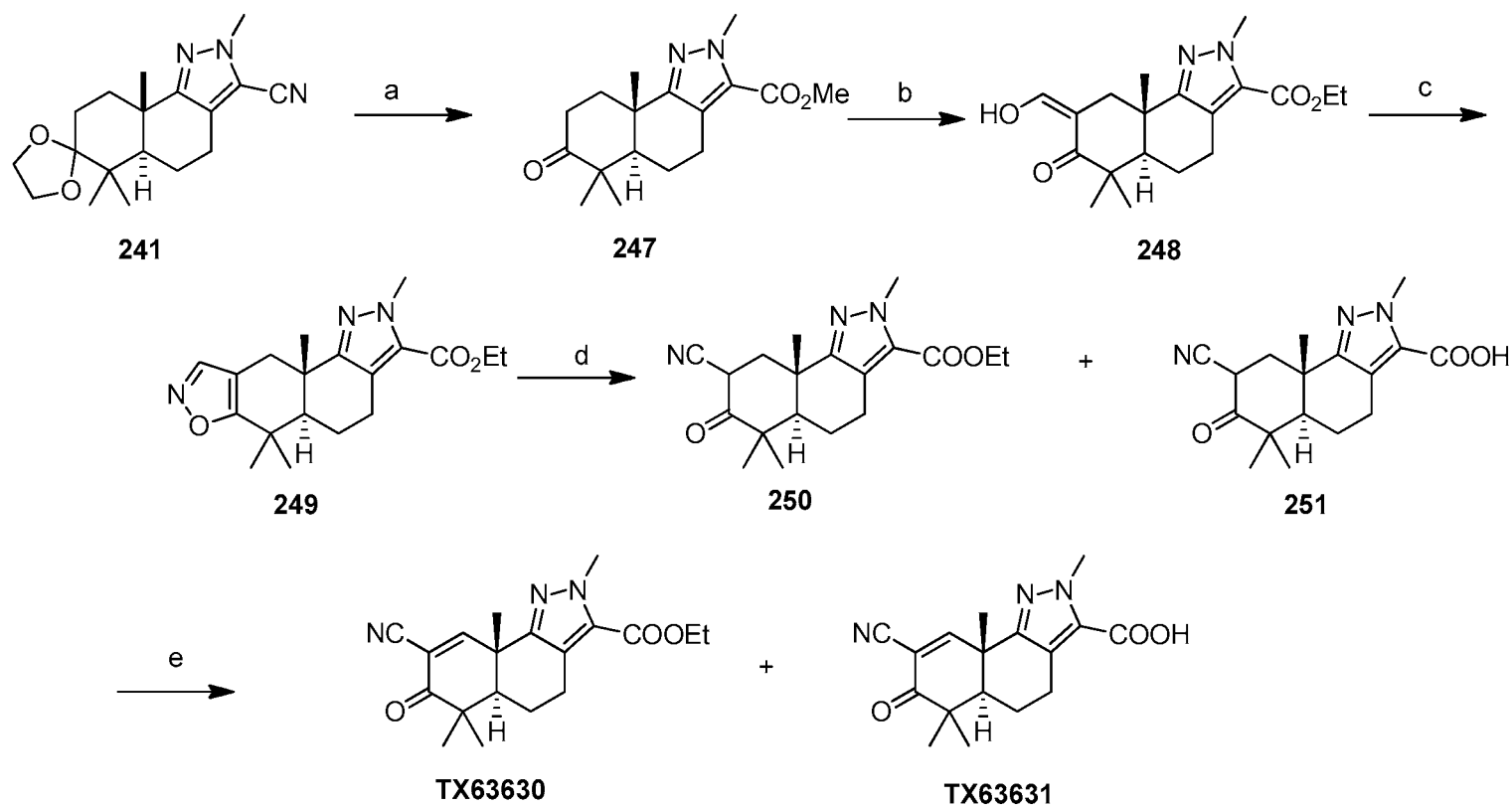
Reagents and conditions pertaining to Schemes 40: (a) TMS-acetylene, CuI, TEA, dioxane, 80°C, 16 hr, 3%; (b) HCl(aq), THF, 3day, 98%; (c) HCO₂Et, NaOMe, 0 °C to RT, 2 h, quantitative; (d) NH₂OH-HCl, 60 °C, 12 h, quantitative; (e) NaOMe, 50 °C, 6 h, 50%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 5 h, 55%.

Scheme 41:



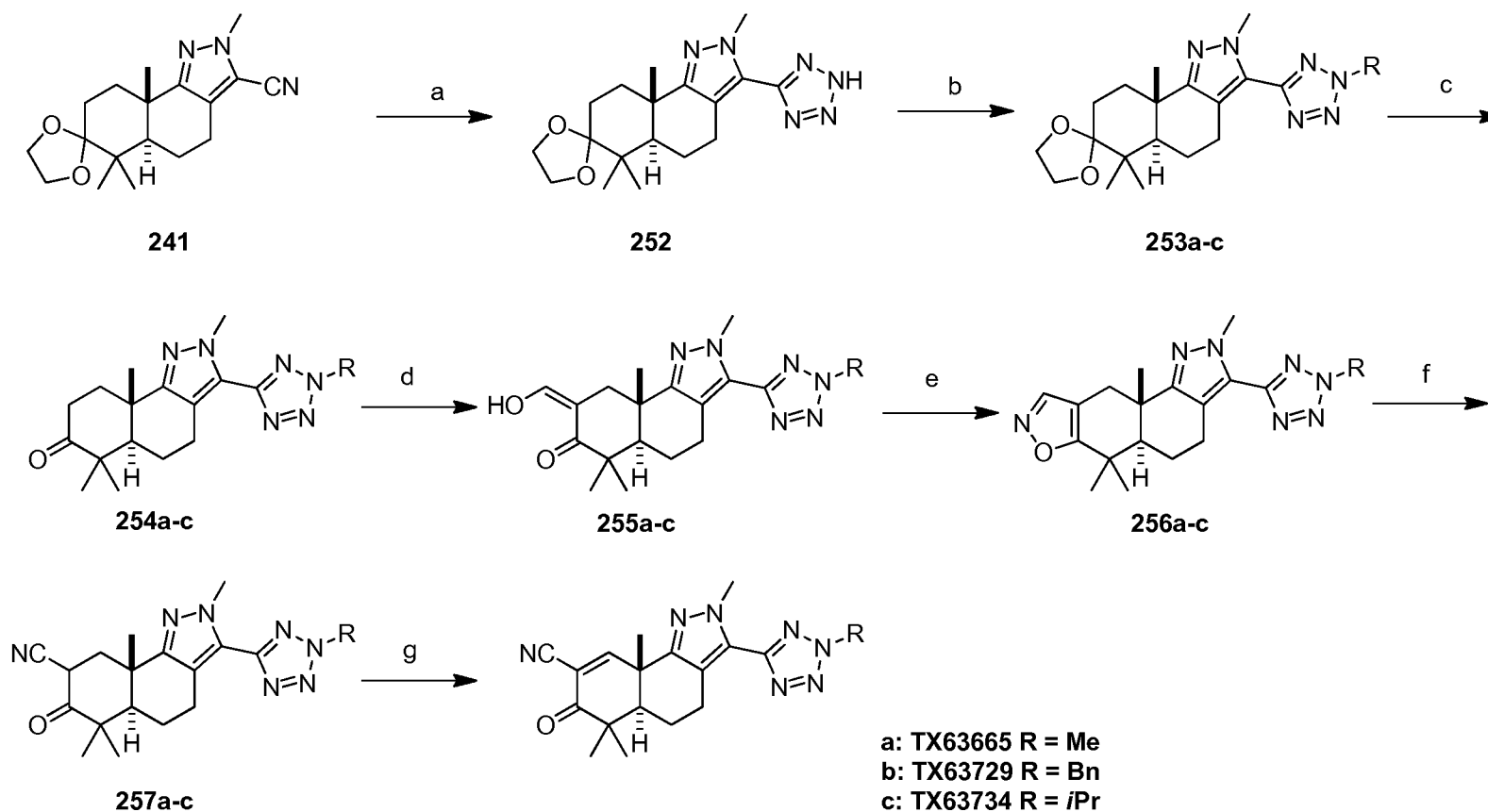
Reagents and conditions pertaining to Schemes 41: (a) $\text{Zn}(\text{CN})_2$, dppf, NaCO_3 , $\text{Pb}(\text{OAc})_2$, DMAc, 120°C , 16 hr, 80%; (b) $\text{HCl}(\text{aq})$, MeOH, 16hr, 96%; (c) HCO_2Et , NaOMe, 0°C to RT, 16h, quantitative; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, 50°C , 16 h, quantitative; (e) NaOMe, THF, MeOH, 50°C , 6 h, 100% as mixture; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C to RT, 2 h; (ii) pyridine, 50°C , 16 h, **TX63613**: 39%, **TX63619**: 8%.

Scheme 42:



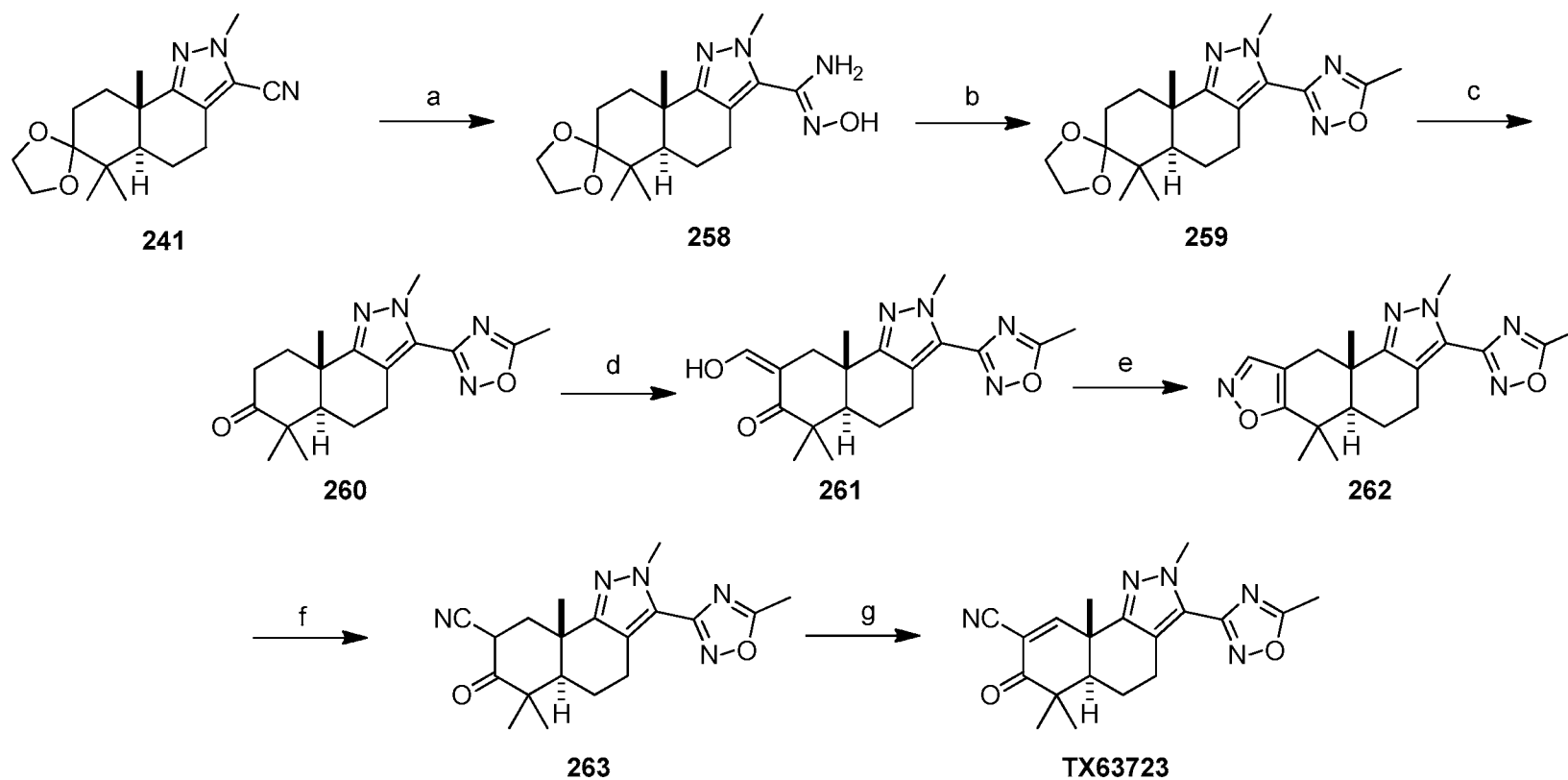
Reagents and conditions pertaining to Schemes 42: (a) HCl, MeOH, 60°C, 16 hr, quantitative; (b) HCO₂Et, NaOMe, RT, 16h, quantitative; (c) NH₂OH-HCl, EtOH, 50 °C, 16 h, quantitative; (d) NaOEt, THF, MeOH, 50 °C, 6 h, 100% as mixture; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 h, **TX63630**: 37%, **TX63631**: 13%.

Scheme 43:



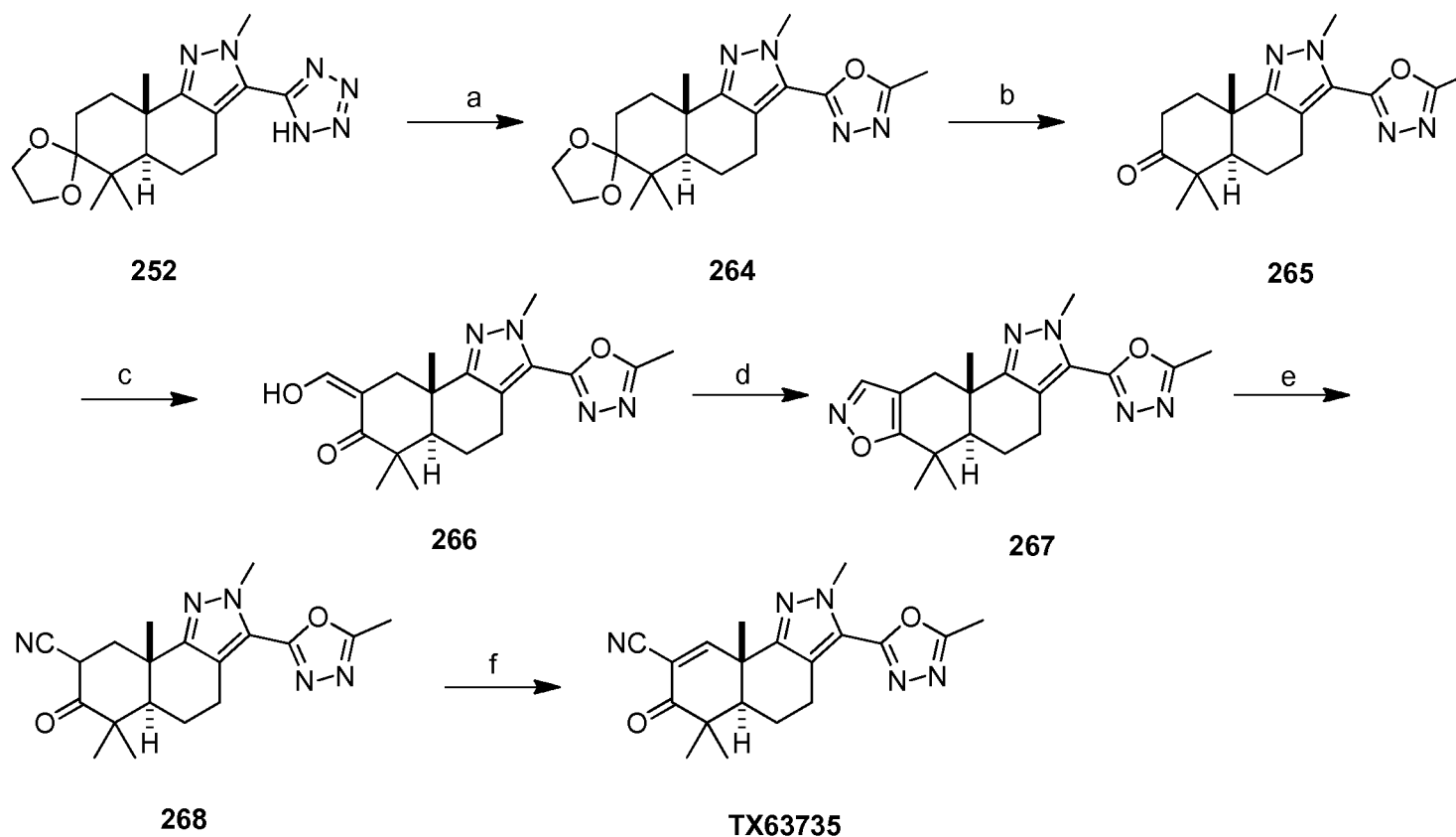
Reagents and conditions pertaining to Schemes 43: (a) TMSN₃, Bu₂SnO, Toluene, 110°C; (b) RX, K₂CO₃, DMF; (c) HCl, THF; (d) HCO₂Et, NaOMe, RT, 16h; (e) NH₂OH-HCl, EtOH, THF, H₂O, 50 °C; (f) NaOMe, THF, MeOH, 50 °C; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 16hr.

Scheme 44:



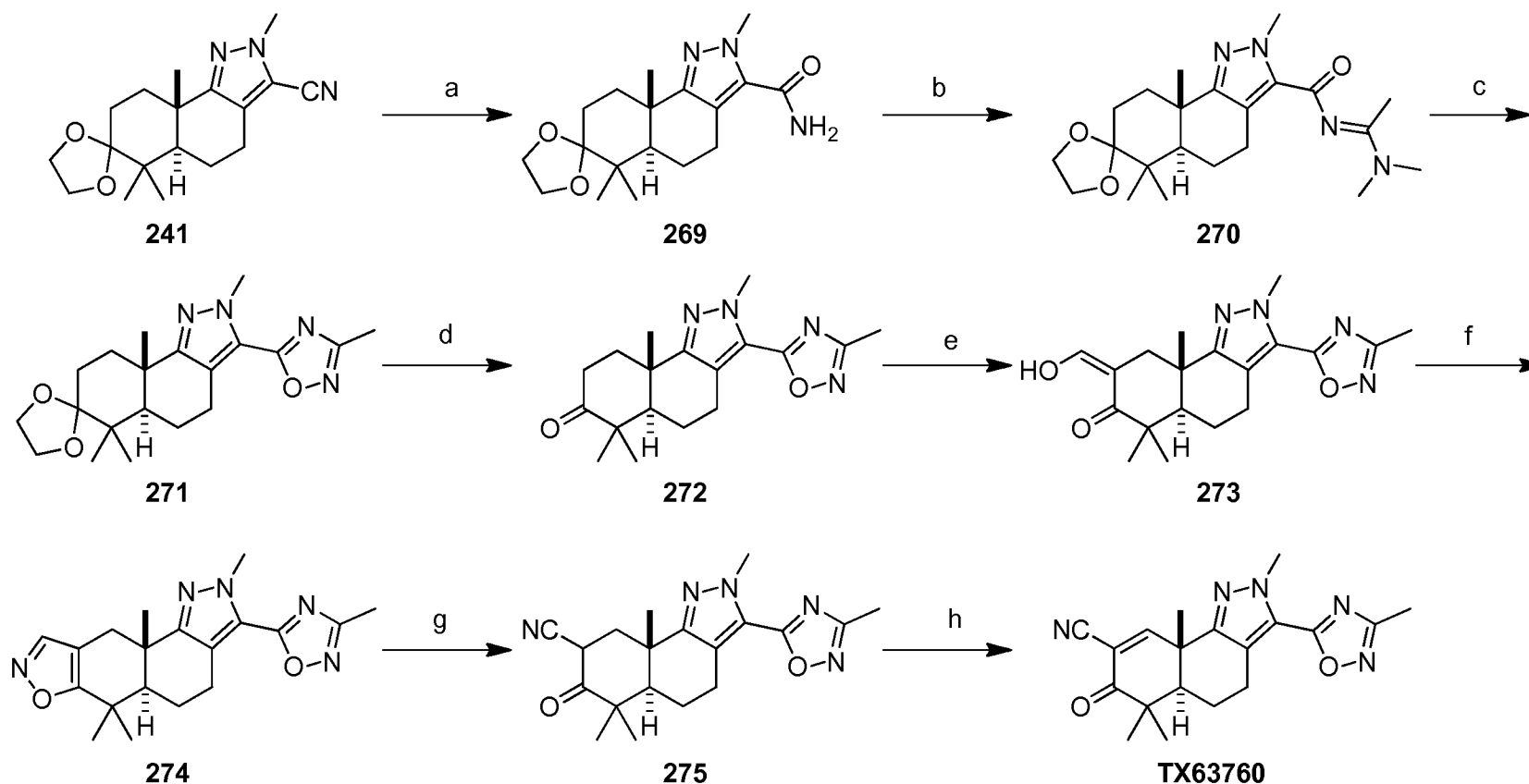
Reagents and conditions pertaining to Schemes 44: (a) NH_2OH , EtOH, 50°C , 16 hr; (b) Dimethylacetamide dimethylacetal, dioxane, 60°C , 2h, 96%; (c) HCl, THF, 2 day, quantitative; (d) HCO_2Et , NaOMe, RT, 16h, quantitative; (e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, THF, H_2O , 50°C , 16 h, 77%; (f) NaOMe, THF, MeOH, 50°C , 3 Hr, 98%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C to RT, 2 h; (ii) pyridine, 60°C , 4 hr, 78%.

Scheme 45:



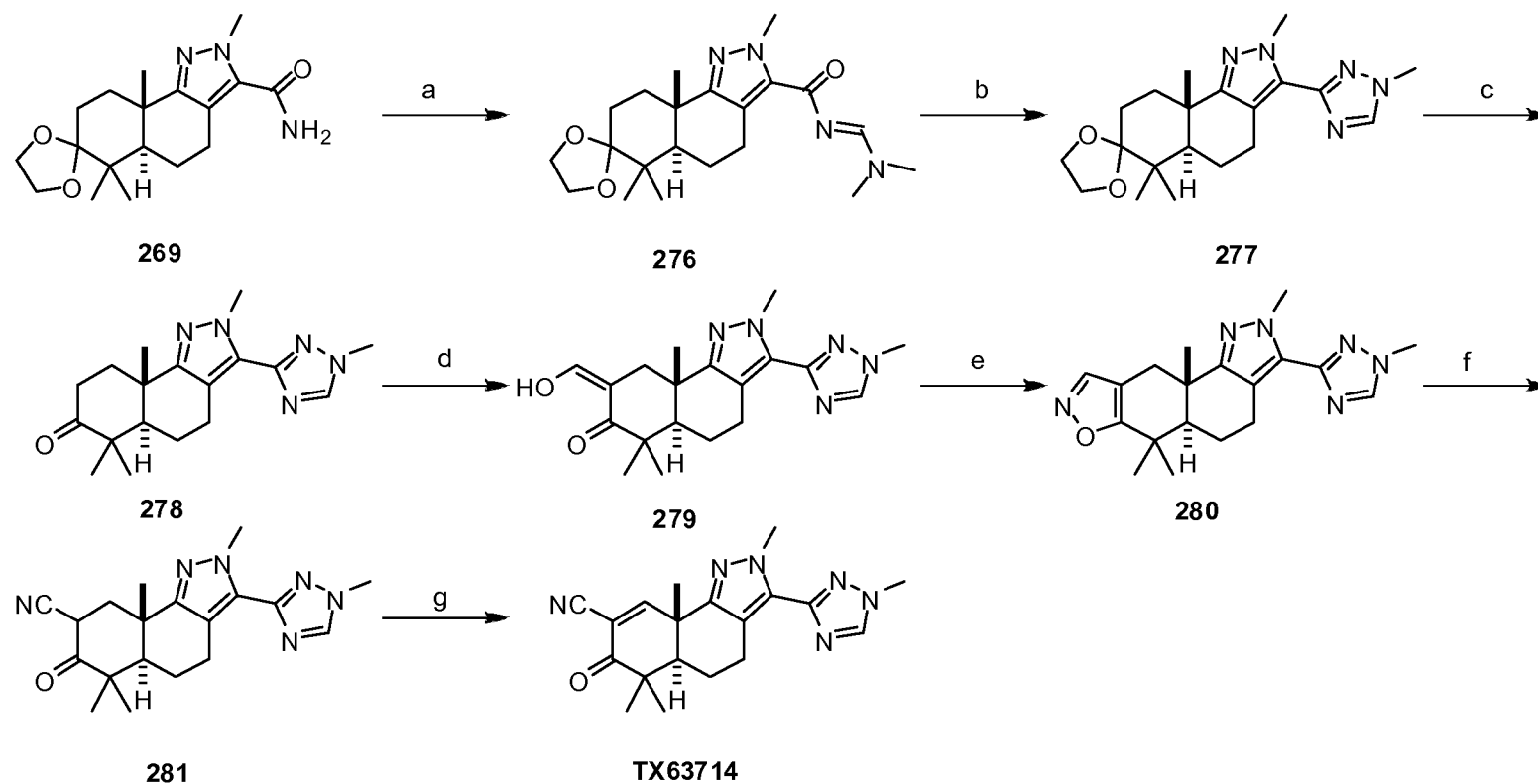
Reagents and conditions pertaining to Schemes 45: (a) Ac_2O , Pyridine, 110°C , 3 hr; (b) HCl(aq) , THF, 2 day, 34%; (c) HCO_2Et , NaOMe, RT, 16h, 99%; (d) $\text{NH}_2\text{OH-HCl}$, EtOH, THF, H_2O , 50°C , 16 h, 28%; (e) NaOMe, THF, MeOH, 50°C , 3 Hr, 100%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C to RT, 2 h; (ii) pyridine, 60°C , 4 hr, 60%.

Scheme 46:



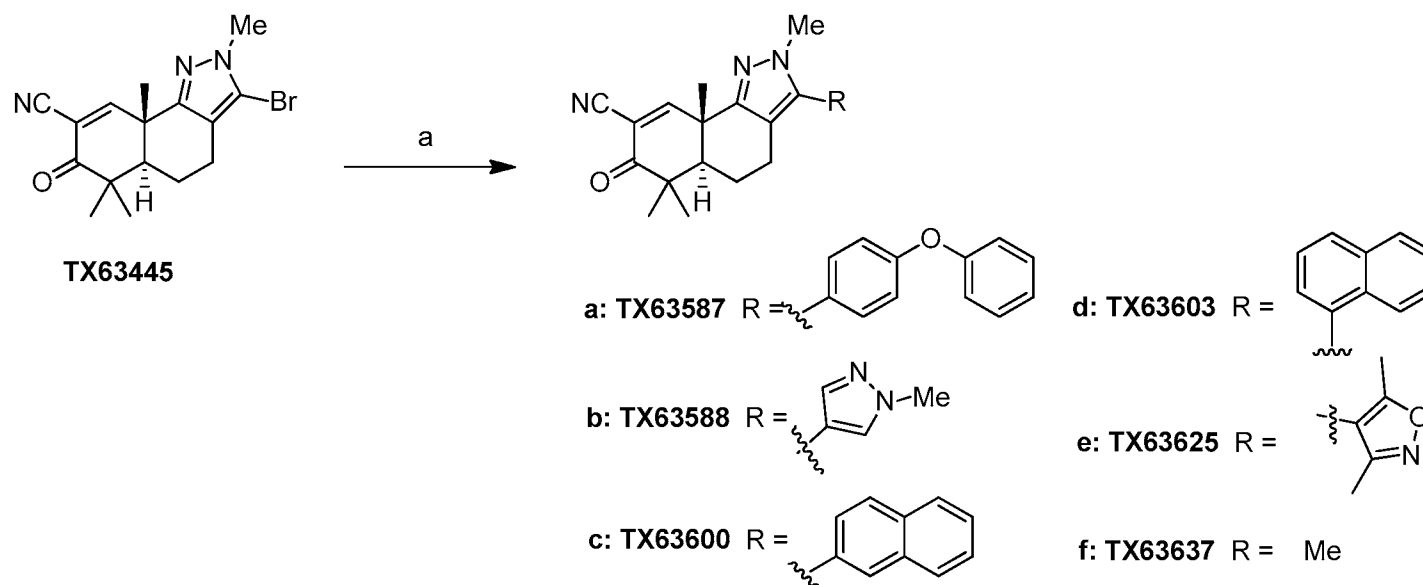
Reagents and conditions pertaining to Schemes 46: (a) Dimethylformamide dimethylacetal, 80°C, 16h; (b) MeNHNH₂, AcOH, Dioxane, 80°C, 2 hr; (c) HCl (aq), THF, quantitative; (d) HCO₂Et, NaOMe, THF, RT, 16h, 97%; (e) NH₂OH-HCl, EtOH, H₂O, 50 °C to RT, 16 h, 79%; (f) NaOMe, THF, MeOH, 50 °C, 3 Hr, 77%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 4 hr, 84%.

Scheme 47:



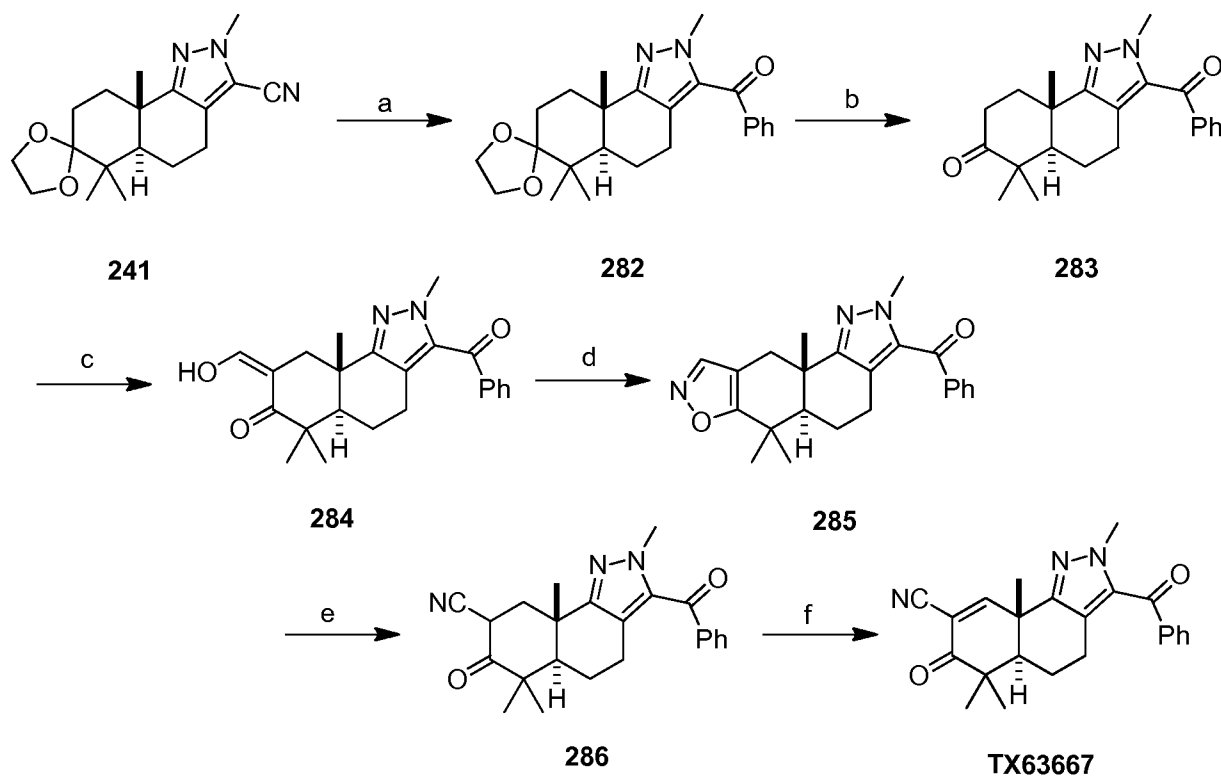
Reagents and conditions pertaining to Schemes 47: (a) KOH, EtOH, H₂O, 3 days, quantitative; (b) Dimethylacetamide dimethylacetal, dioxane, 80°C, 2h; (c) NH₂OH-HCl, TEA, AcOH, Dioxane, 80°C, 3 hr, 58%; (d) HCl (aq), THF, quantitative; (e) HCO₂Et, NaOMe, THF, RT, 16h, 97%; (f) NH₂OH-HCl, EtOH, THF, H₂O, 50 °C, 16 h, 94%; (g) NaOMe, THF, MeOH, 50 °C, 3 Hr, 79%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 6 hr, 71%

Scheme 48:



Reagents and conditions pertaining to Schemes 48: (a) R-B(OH)₂, K₃PO₄, Pd(PPh₃)₄, dimethoxyethane, 80 °C, 16 hr.

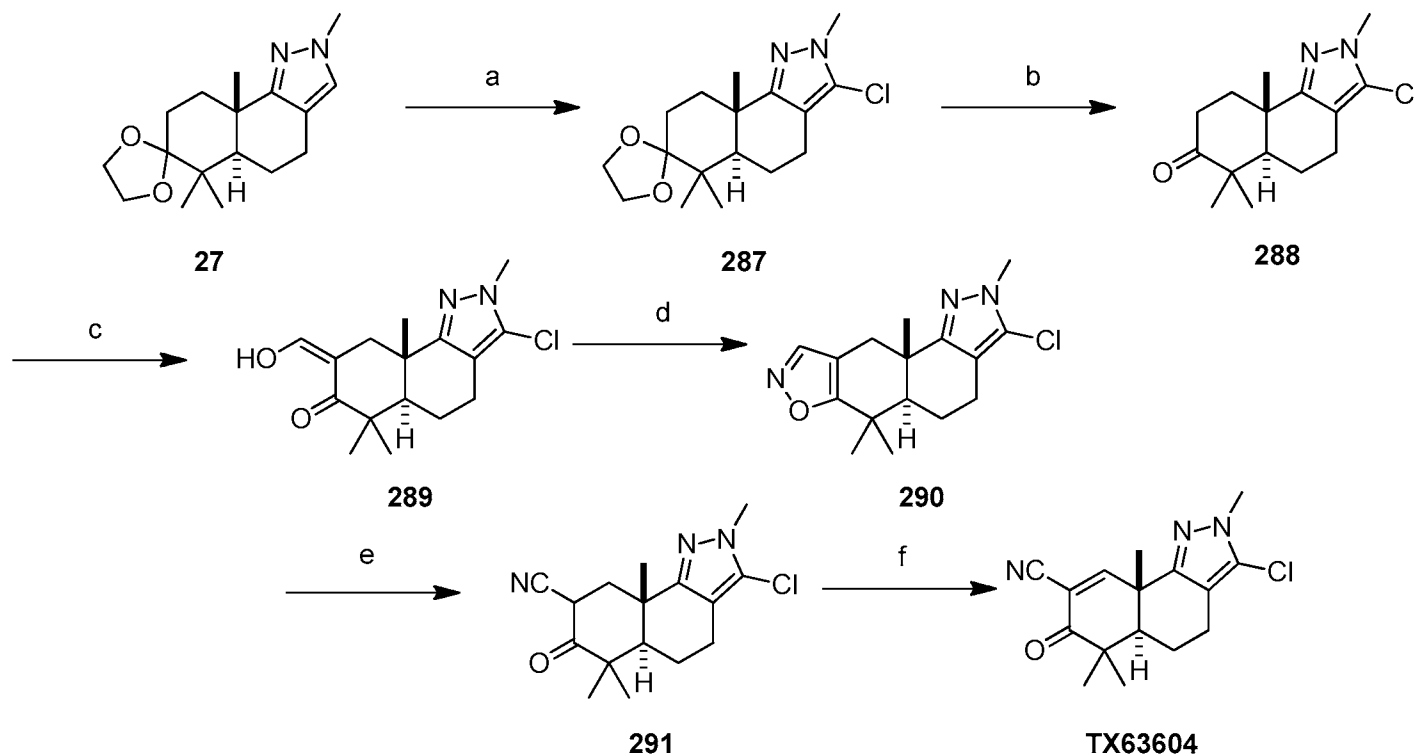
Scheme 49:



Reagents and conditions pertaining to Schemes 49: (a) PhMgBr, THF, 0 °C to RT, 16 hr; (b) HCl (aq), THF, RT, 16 hr then 60 °C, 4Hr, 93%; (c) HCO₂Et, NaOMe, RT, 16h, 97%; (d) NH₂OH-HCl, TEA, AcOH, Dioxane, 50°C, 4 hr, 98%; (e) NaOMe, THF, MeOH, 50 °C, 16 Hr, 83%; (f) (i)

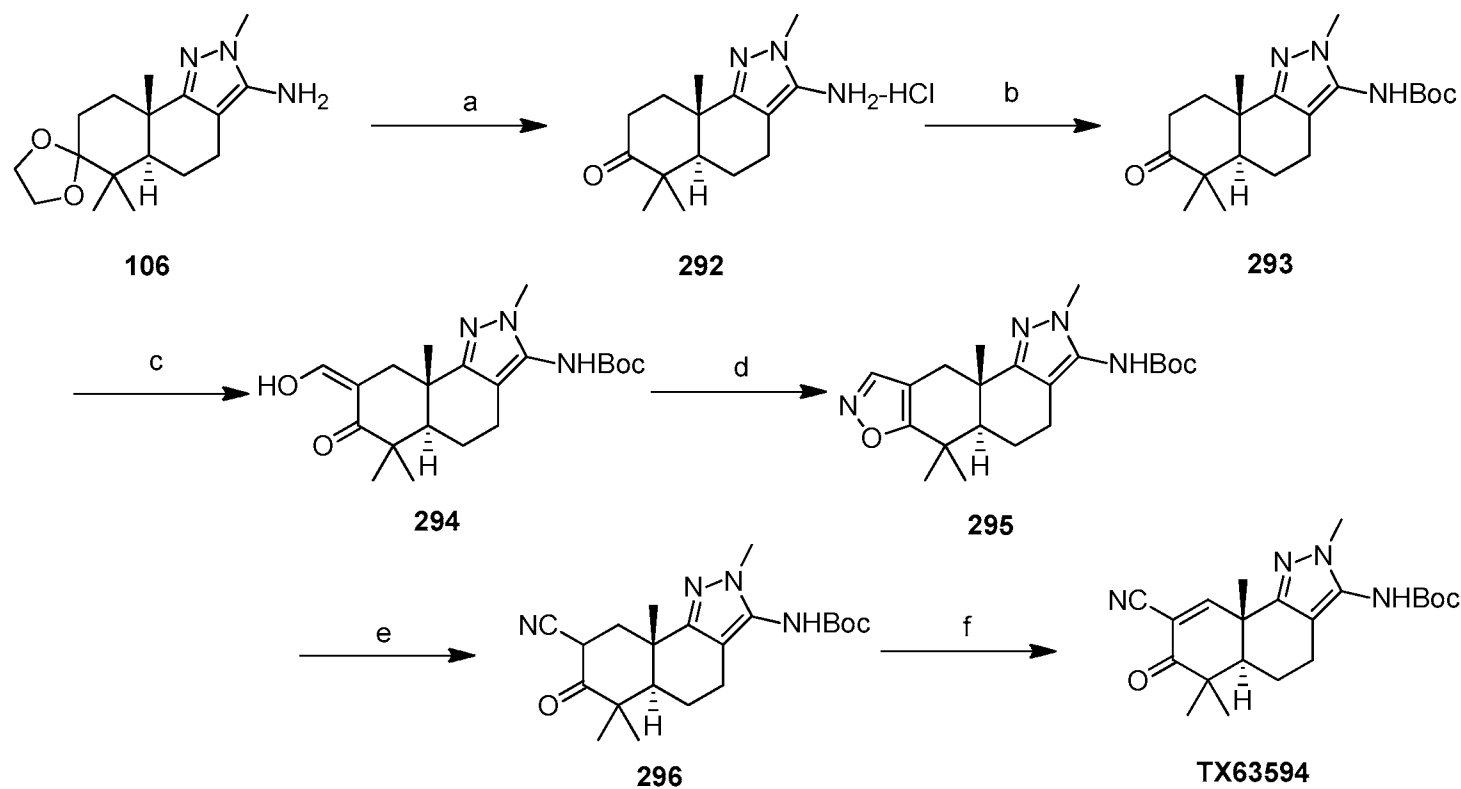
5 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, 90%

Scheme 50:

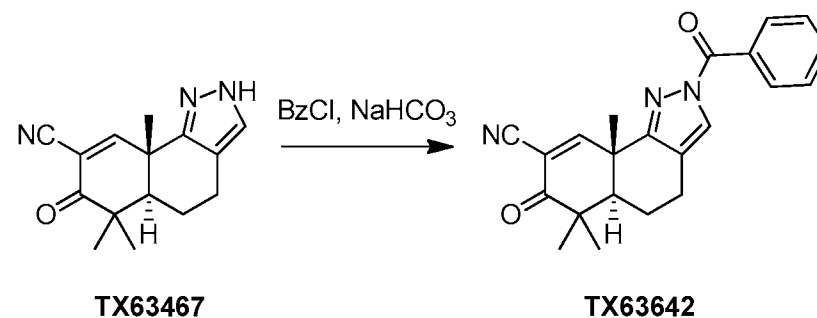


Reagents and conditions pertaining to Schemes 50: (a) NCS, DCM, RT, 4 day; (b) HCl (aq), THF, RT, 3 hr, 76%; (c) HCO₂Et, NaOMe, RT, 16h, 91%; (d) NH₂OH-HCl, EtOH, H₂O, 50°C, 16 hr, 50%; (e) NaOMe, THF, MeOH, 50 °C, 16 Hr; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, 60%.

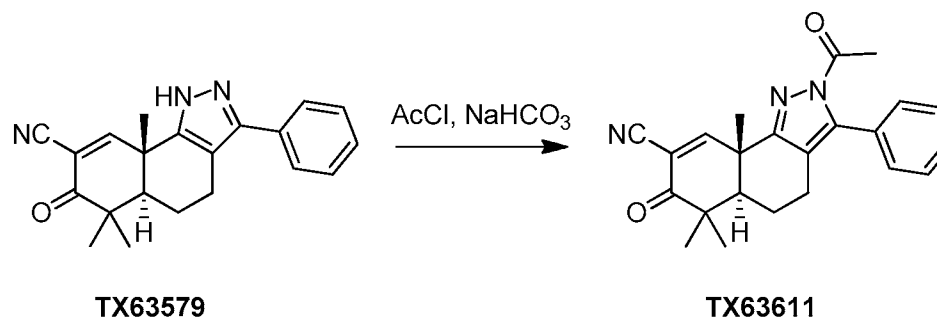
Scheme 51:



Reagents and conditions pertaining to Schemes 51: (a) HCl (aq), THF, RT, 3 hr; (b) (Boc)₂O, DMAP, TEA, dioxane, H₂O, RT, 16 hr, (c) HCO₂Et, NaOMe, RT, 16h; (d) NH₂OH-HCl, TEA, EtOH, H₂O, Py-Ts, 50°C, 4 hr; (e) NaOMe, THF, MeOH, 50 °C, 16 Hr, 78%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, 12.5%.

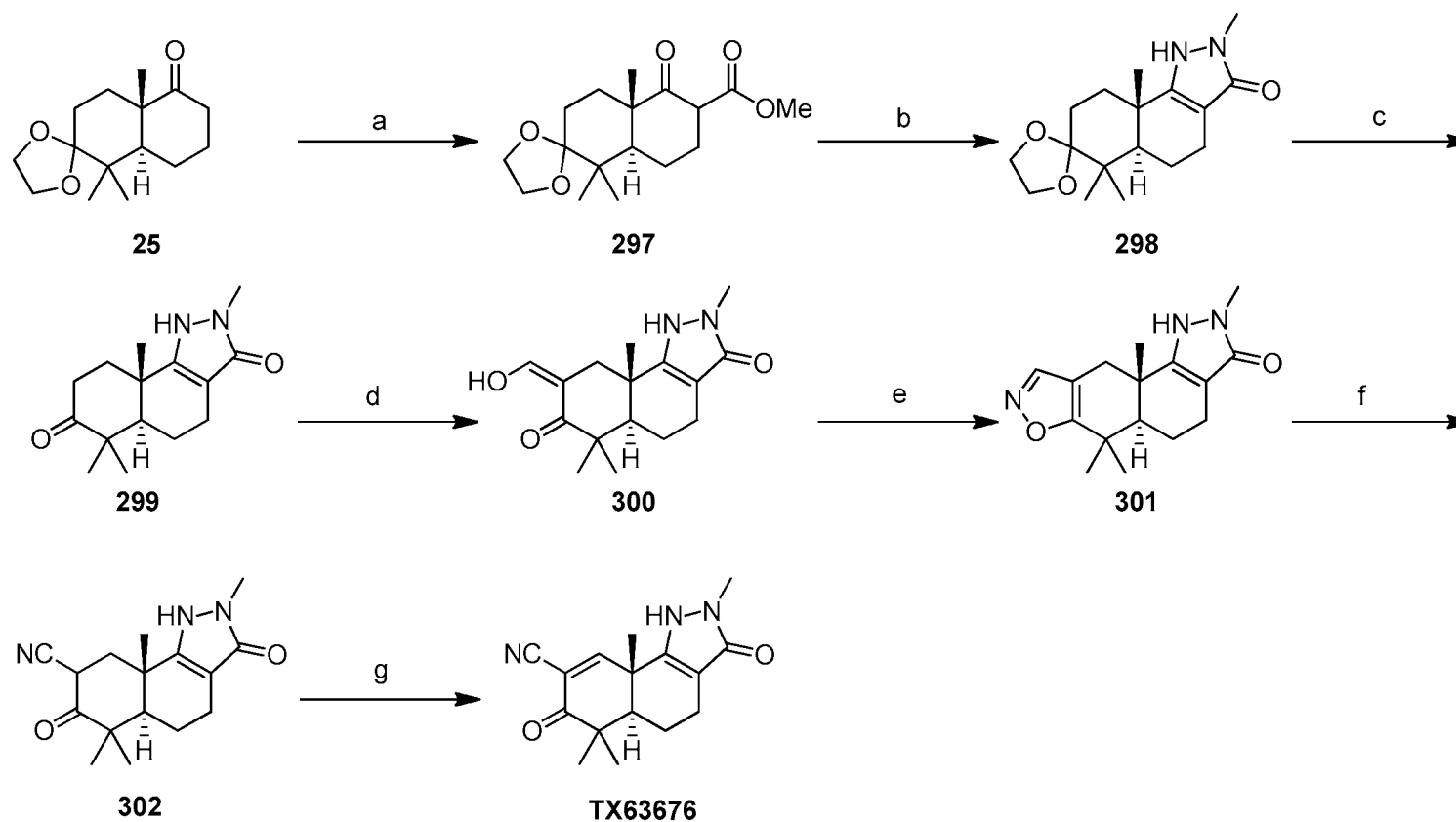
Scheme 52:

Reagents and conditions pertaining to Scheme 52: (a) BzCl, NaHCO₃ (aq), THF, 0 °C, 47%.

Scheme 53:

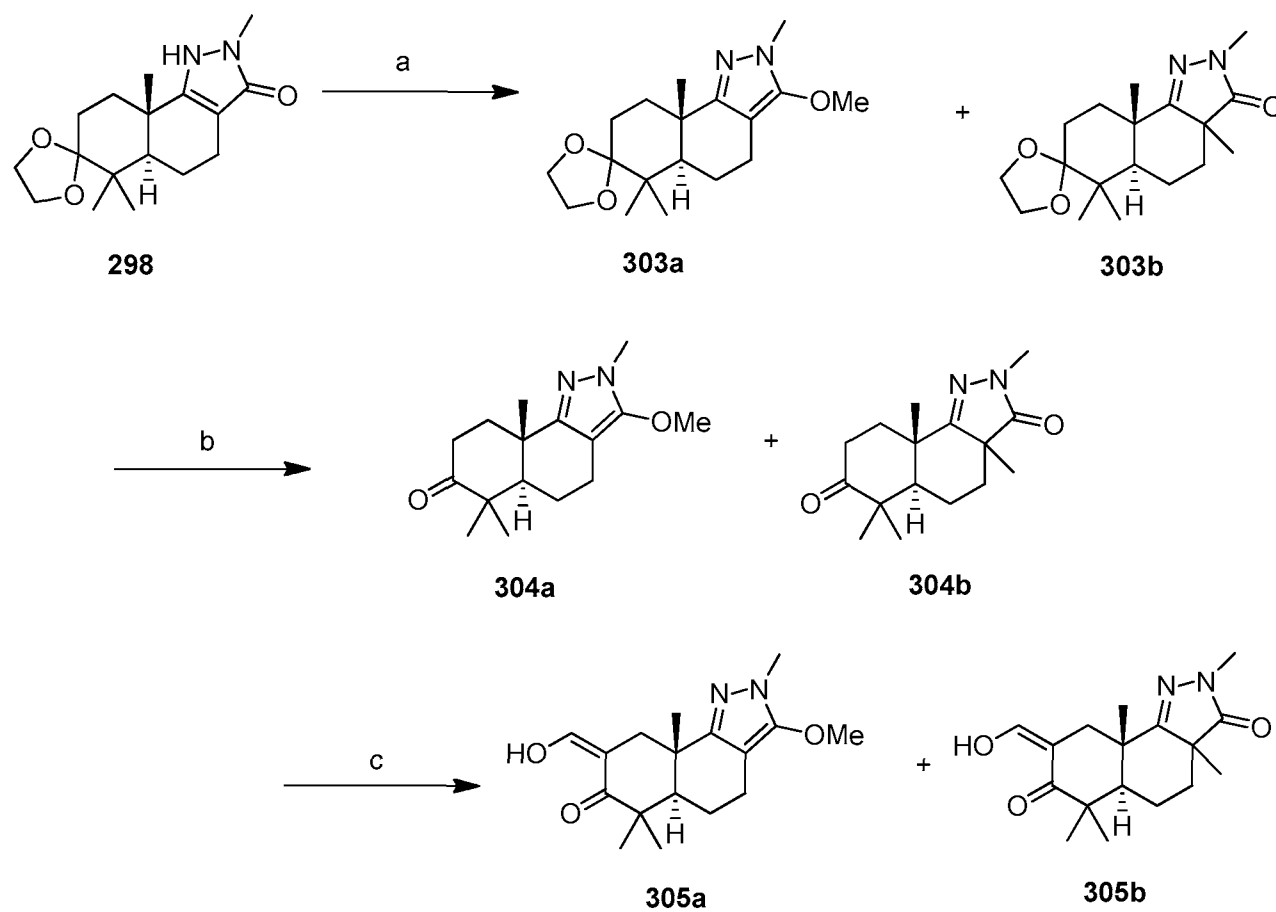
Reagents and conditions pertaining to Scheme 53: (a) BzCl, NaHCO₃ (aq), THF, 0 °C, 47%.

Scheme 54:

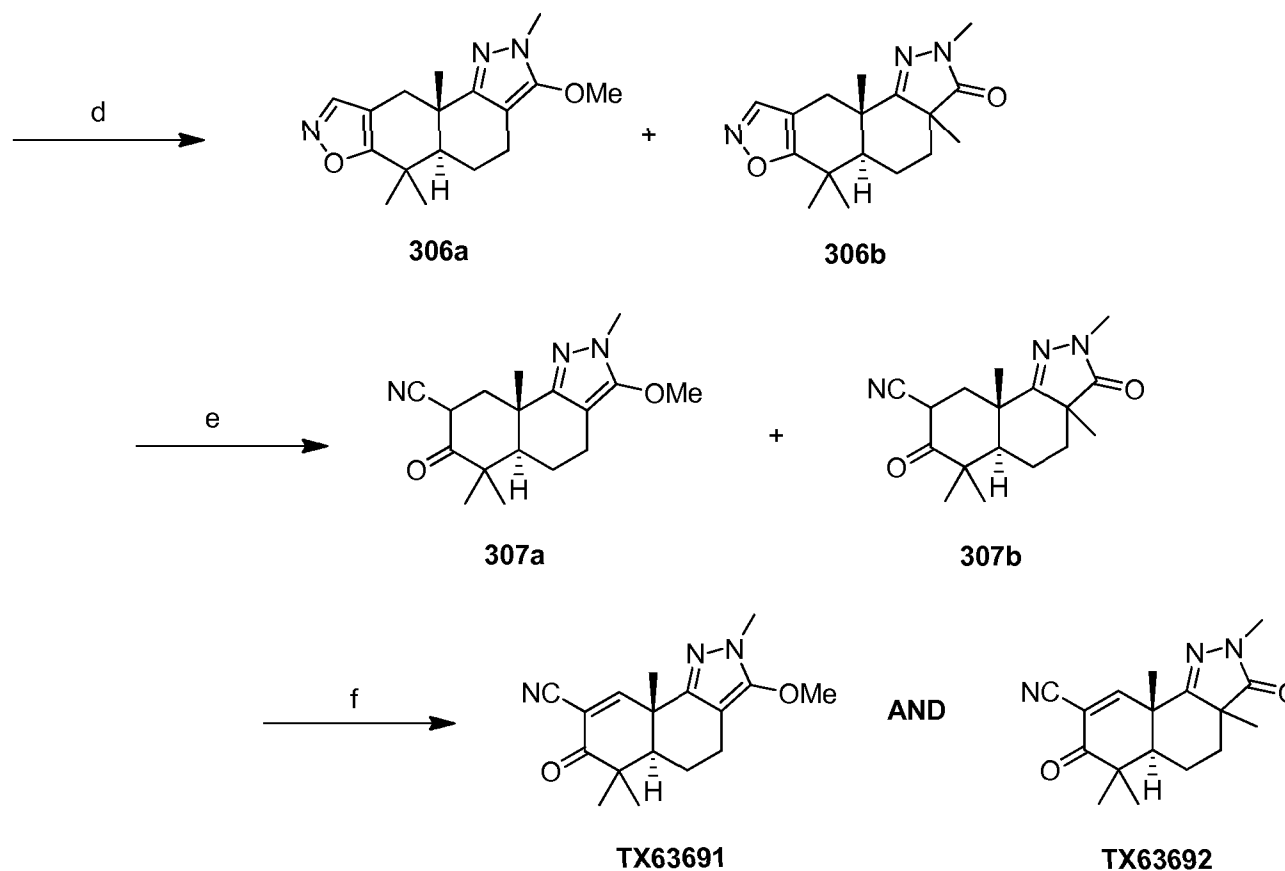


Reagents and conditions pertaining to Schemes 54: (a) $(\text{MeO})_2\text{CO}$, NaH, THF, reflux, 3 hr, 87%; (b) MeNHNH_2 , EtOH, 60°C , 16 hr, (c) HCl (aq), MeOH, 16 hr, 100%; (d) HCO_2Et , NaOMe, RT, 16h, 100%; (e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 50°C , 16 hr, 100%; (f) NaOMe, MeOH, 50°C , 9 Hr, 99%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C to RT, 2 h; (ii) pyridine, 55°C , 5 hr, 9%.

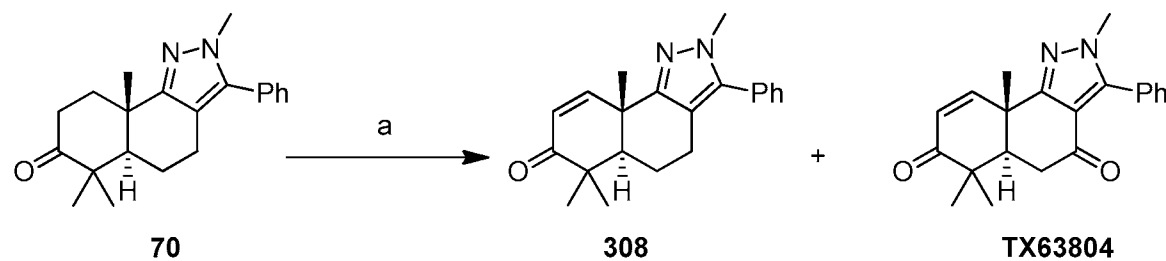
Scheme 55a:



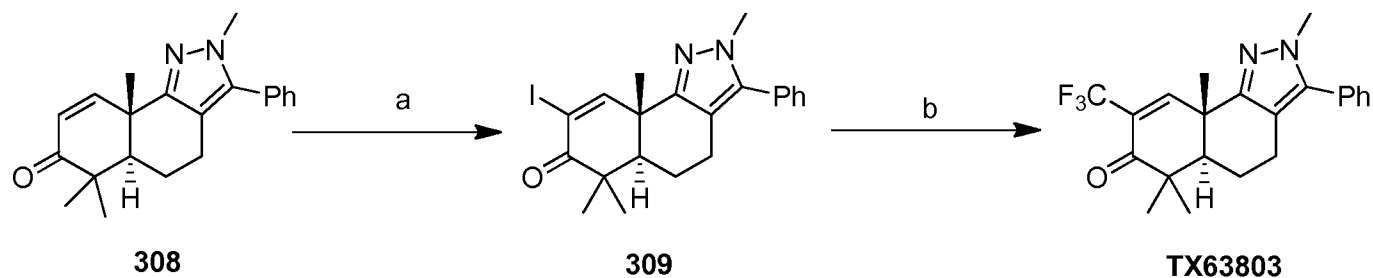
Scheme 55b:



Reagents and conditions pertaining to Schemes 55(a) and (b): (a) MeI, K₂CO₃, DMF, 16 hr, 64%; (b) HCl (aq), MeOH, 16 hr, 100%; (c) HCO₂Et, NaOMe, RT, 16h, 100%; (d) NH₂OH-HCl, EtOH, 50°C, 16 hr, 100%; (e) NaOMe, THF/MeOH, 50 °C, 6 Hr, 100%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, 15%.

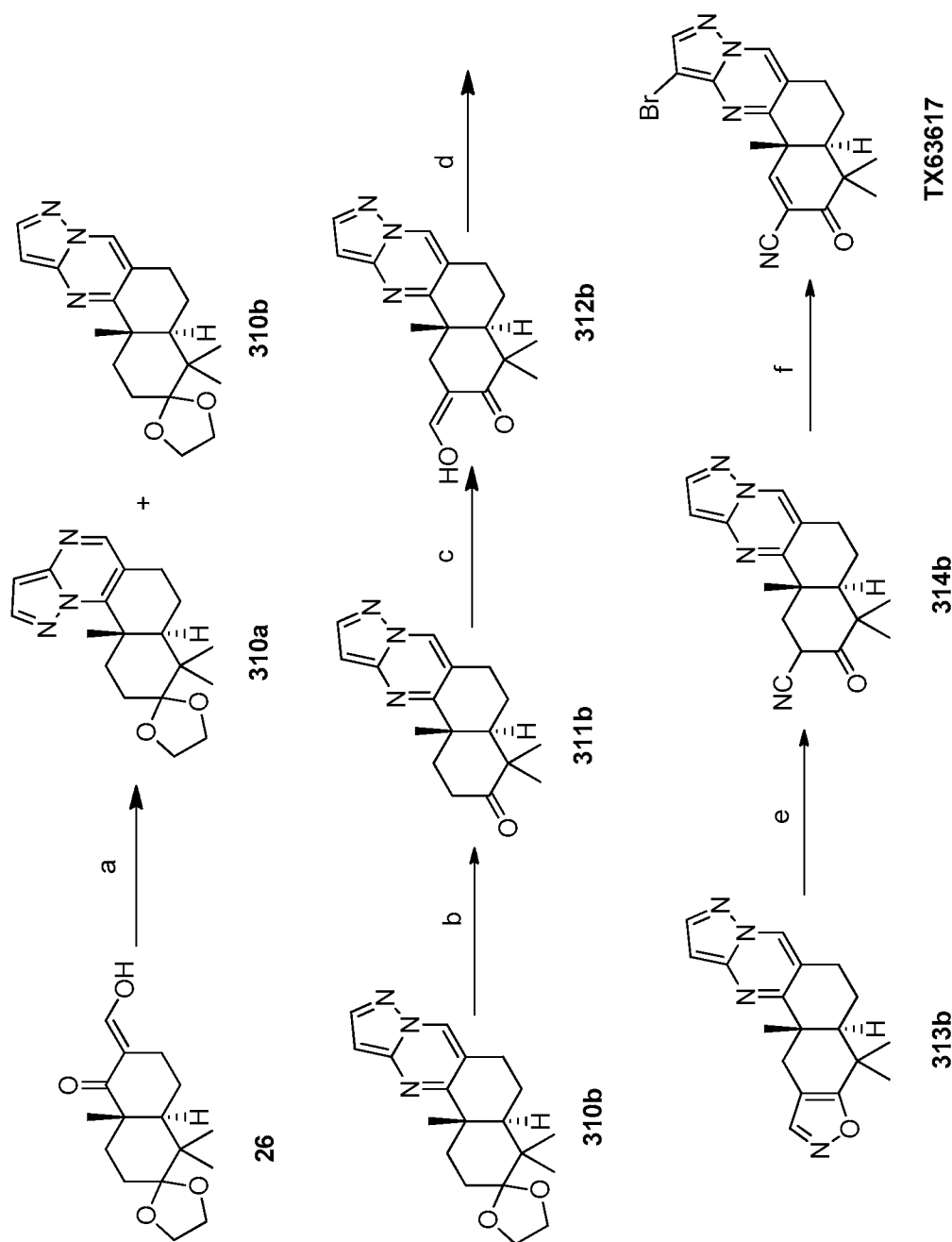
Scheme 56:

Reagents and conditions pertaining to Scheme 56: (a) IBX, DMF, 65 °C, 6 hr, **308**: 60%, **TX63804**: 3%.

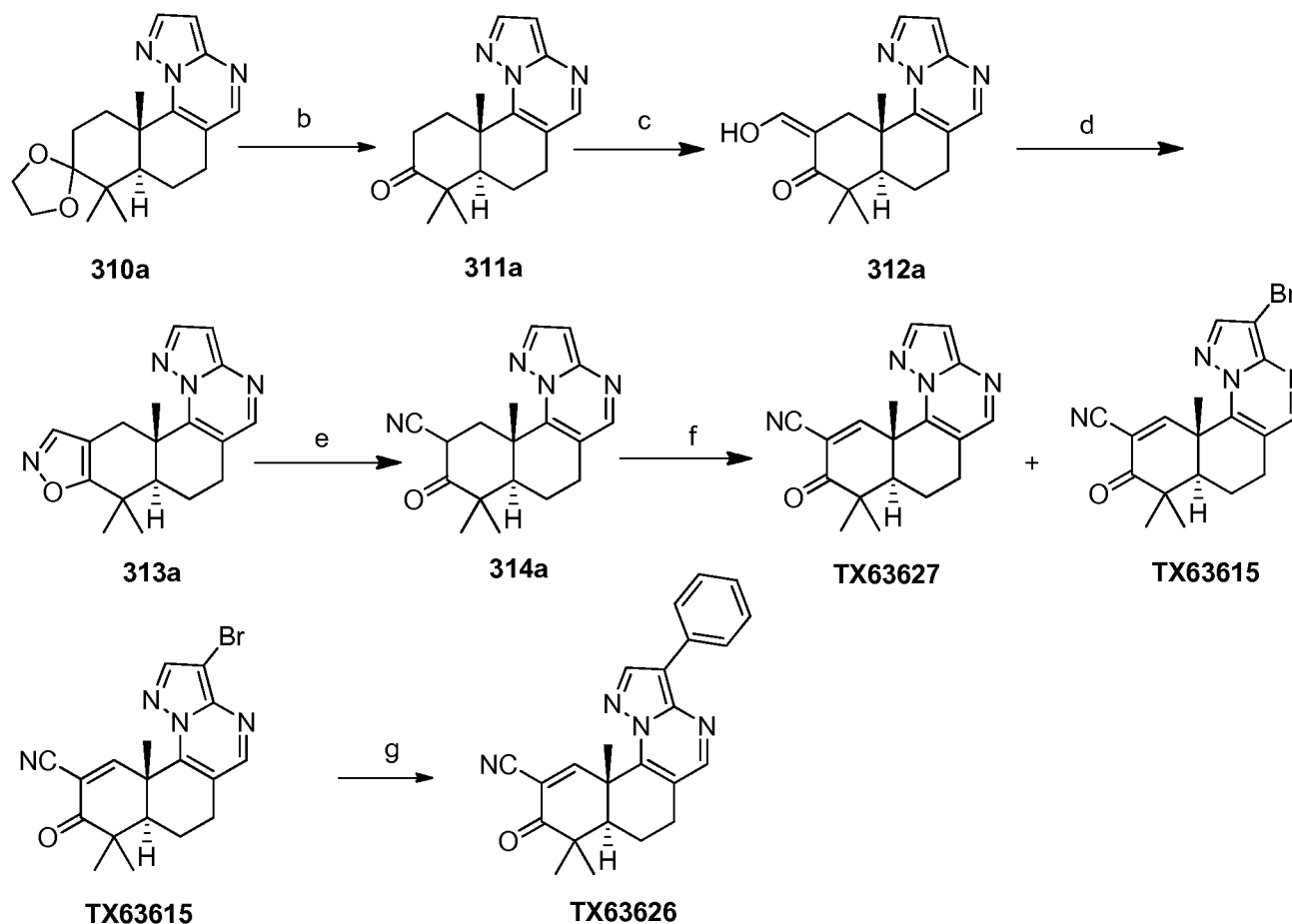
Scheme 57:

Reagents and conditions pertaining to Scheme 57: (a) I₂, THF, Pyridine, 60 °C, 16 hr, 100%; (b) FSO₂CF₂CO₂Me, CuI, HMPA, DMF, 70 °C, 6 hr, 63%.

Scheme 58(a):

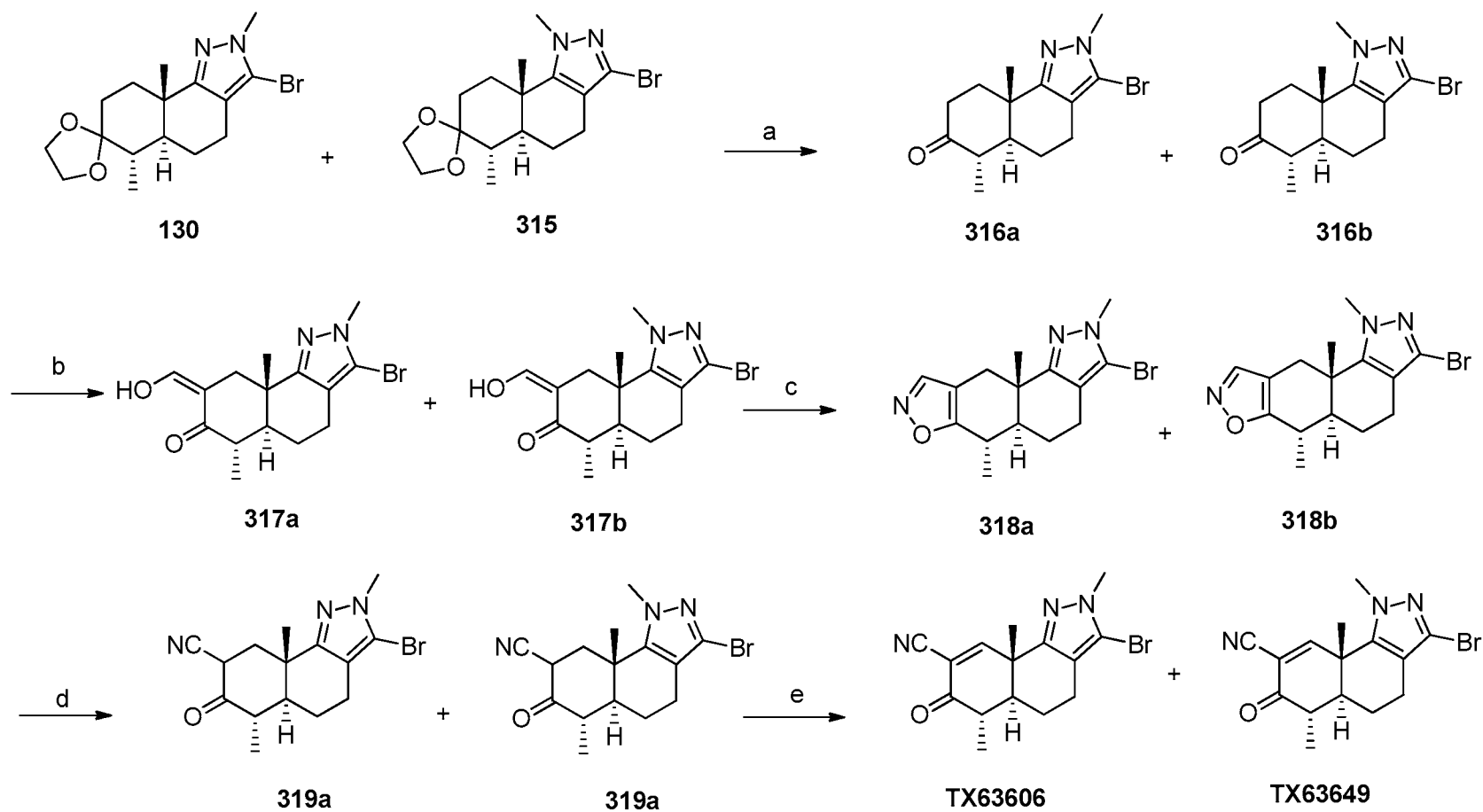


Scheme 58(b):



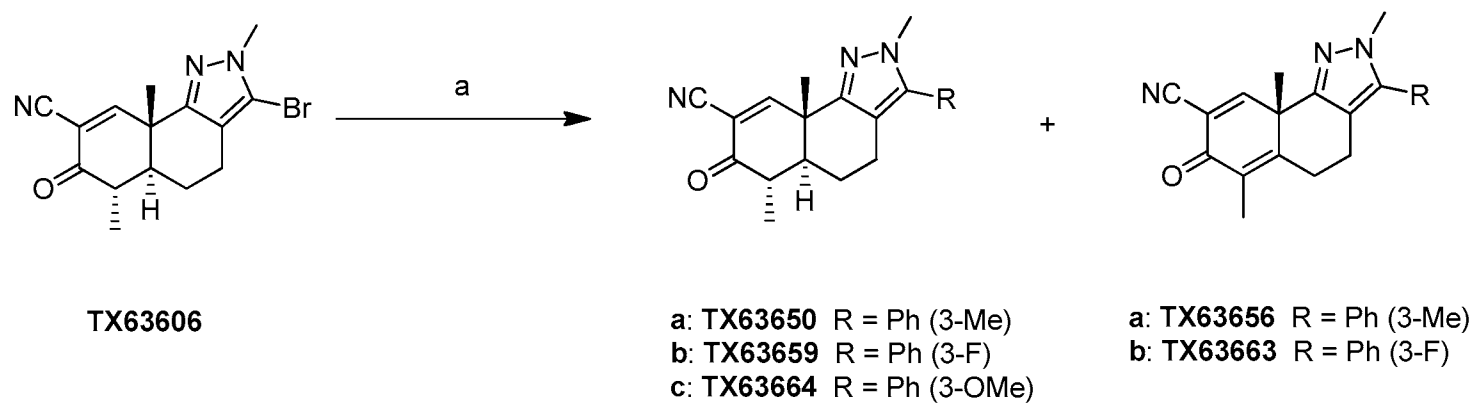
Reagents and conditions pertaining to Schemes 58 (a) and (b): (a) 3-aminopyrazole, (TsO)₂O, toluene, reflux, 16 hr, **310a**: 49%, **310b**: 6.7%; (b) HCl (aq), MeOH, **311a**: 100%, **311b**: 90%; (c) HCO₂Et, NaOMe, RT; (d) NH₂OH-HCl, EtOH, 50°C; (e) NaOMe, THF/MeOH, 50 °C; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, **TX63617**: 33%, and **TX63627**: 17%, **TX63615**: 24%; (g) PhB(OH)₂, Pd(PPh₃)₄, DME, K₃PO₄, 90 °C, 16 hr, 26%.

Scheme 59:



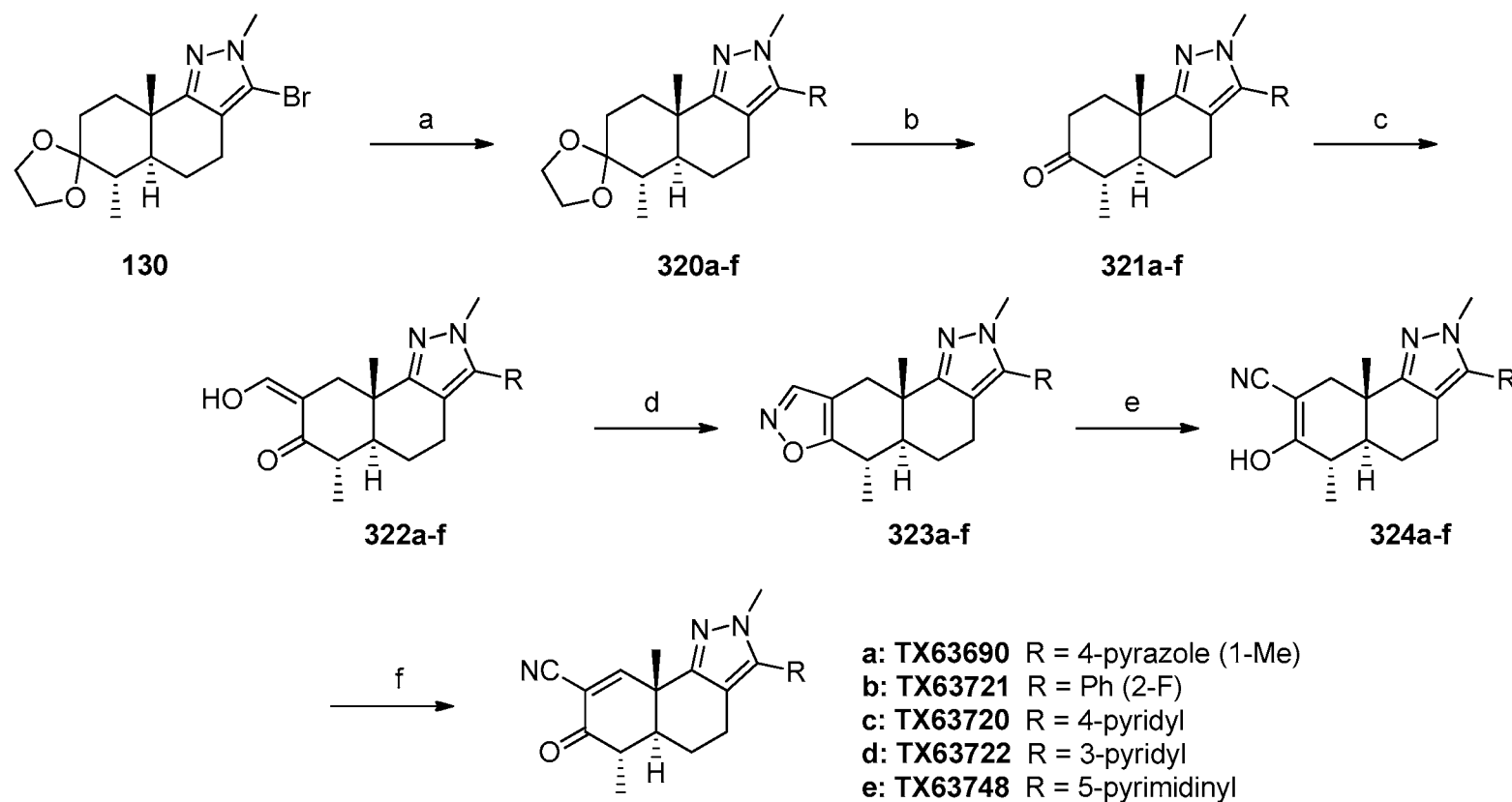
Reagents and conditions pertaining to Schemes 59: (a) HCl (aq), MeOH; (b) HCO₂Et, NaOMe, RT; (c) NH₂OH-HCl, EtOH, 50°C; (d) NaOMe, THF/MeOH, 50 °C; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, **TX63606**: 69%, **TX63649**: 2%.

Scheme 60:



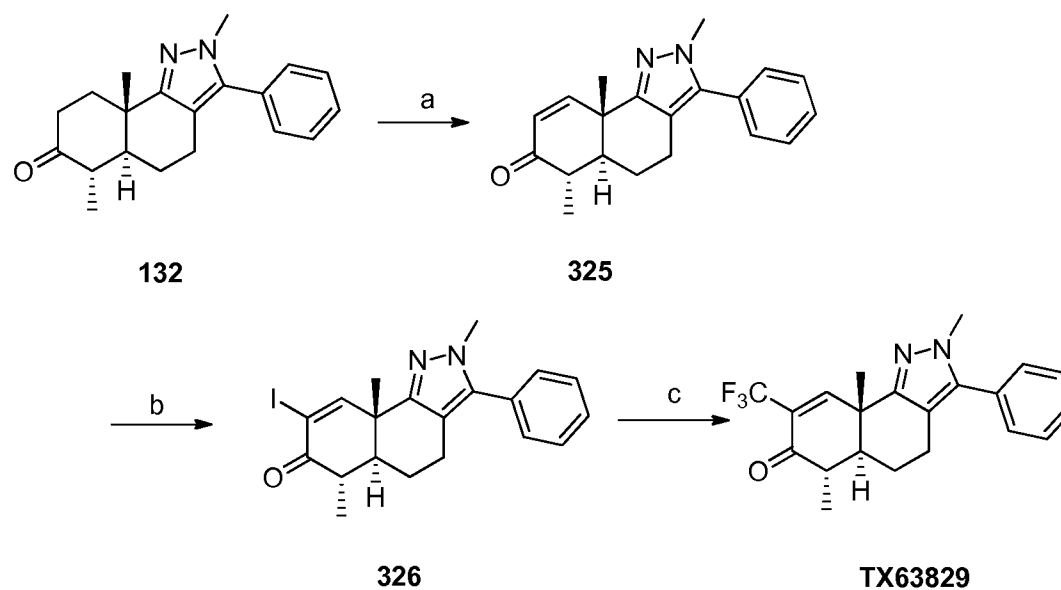
Reagents and conditions pertaining to Scheme 60: (a) R-B(OH)₂, K₃PO₄, Pd(PPh₃)₄, DME, 80 °C, 16 hr.

Scheme 61:



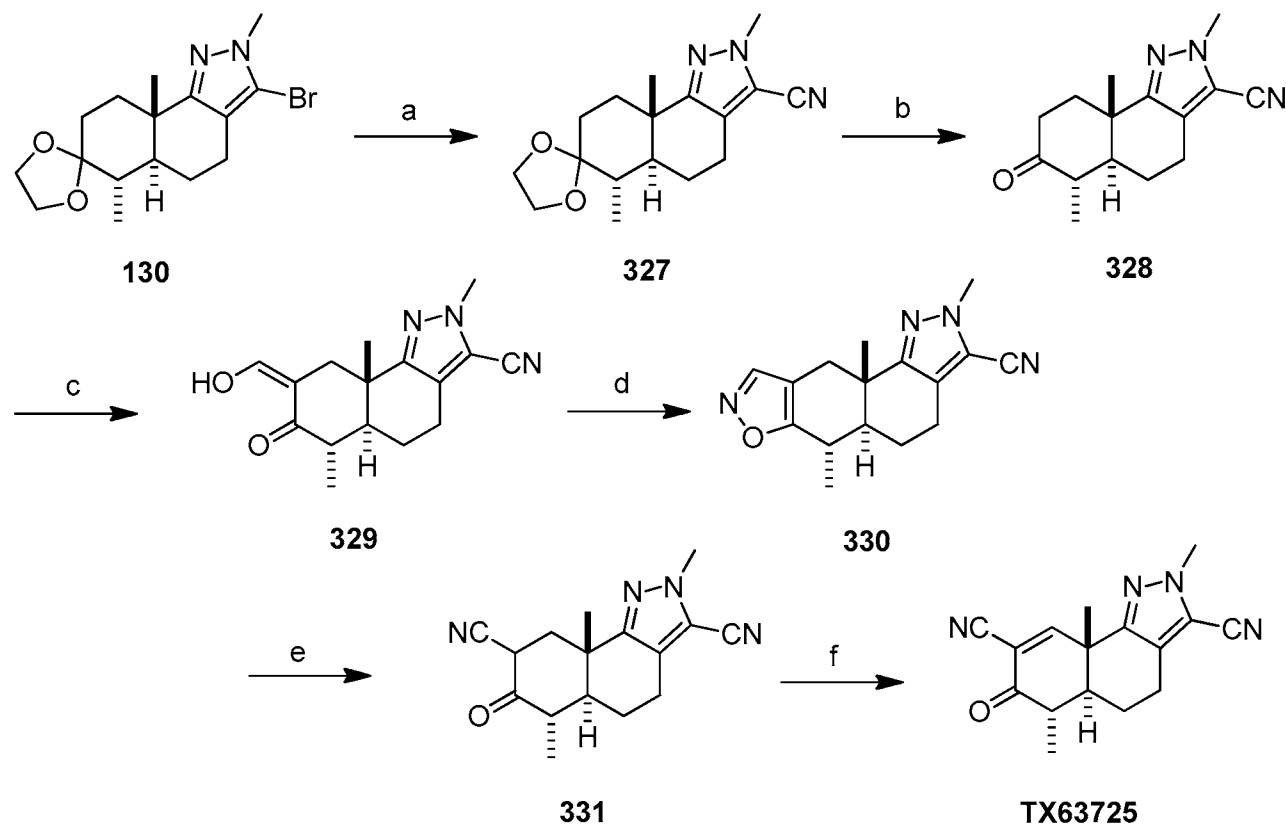
Reagents and conditions pertaining to Schemes 61: (a) R-B(OH)₂, K₃PO₄, PPh₃, Pd(OAc)₂ or Pd(PPh₃)₄, DME, 80 °C, 16 hr; (b) HCl (aq), MeOH; (c) HCO₂Et, NaOMe, RT; (d) NH₂OH-HCl, EtOH, 50°C; (e) NaOMe, THF/MeOH, 50 °C; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr.

Scheme 62:



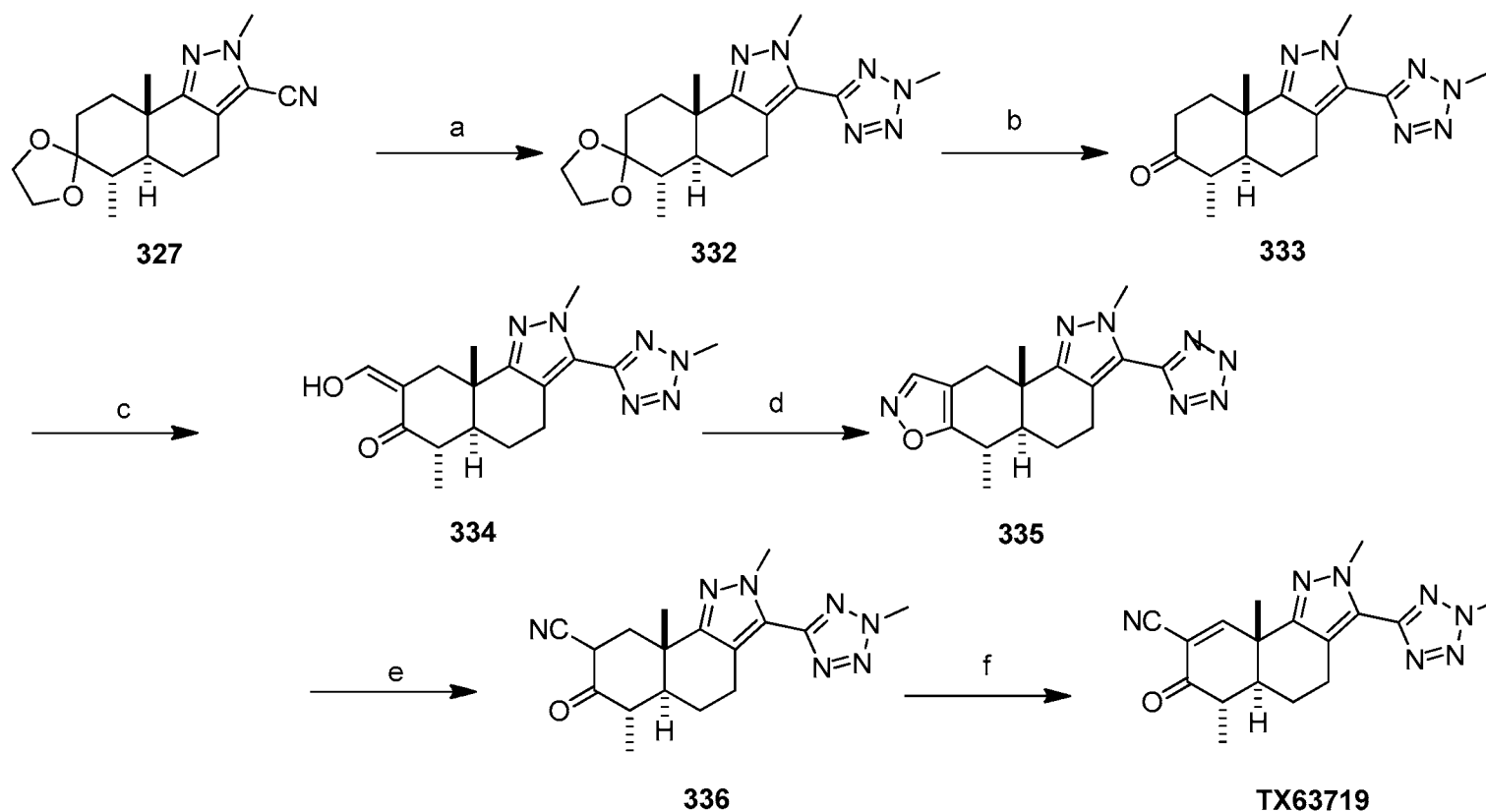
Reagents and conditions pertaining to Schemes 62: (a) IBX, DMSO, 65 °C, 7 hr, 43%; (b) I₂, Pyridine, THF, 60 °C, 30 hr, 100%; (c) FSO₂CF₂CO₂Me, CuI, HMPA, DMF, 70 °C, 6 hr, 42%.

Scheme 63:



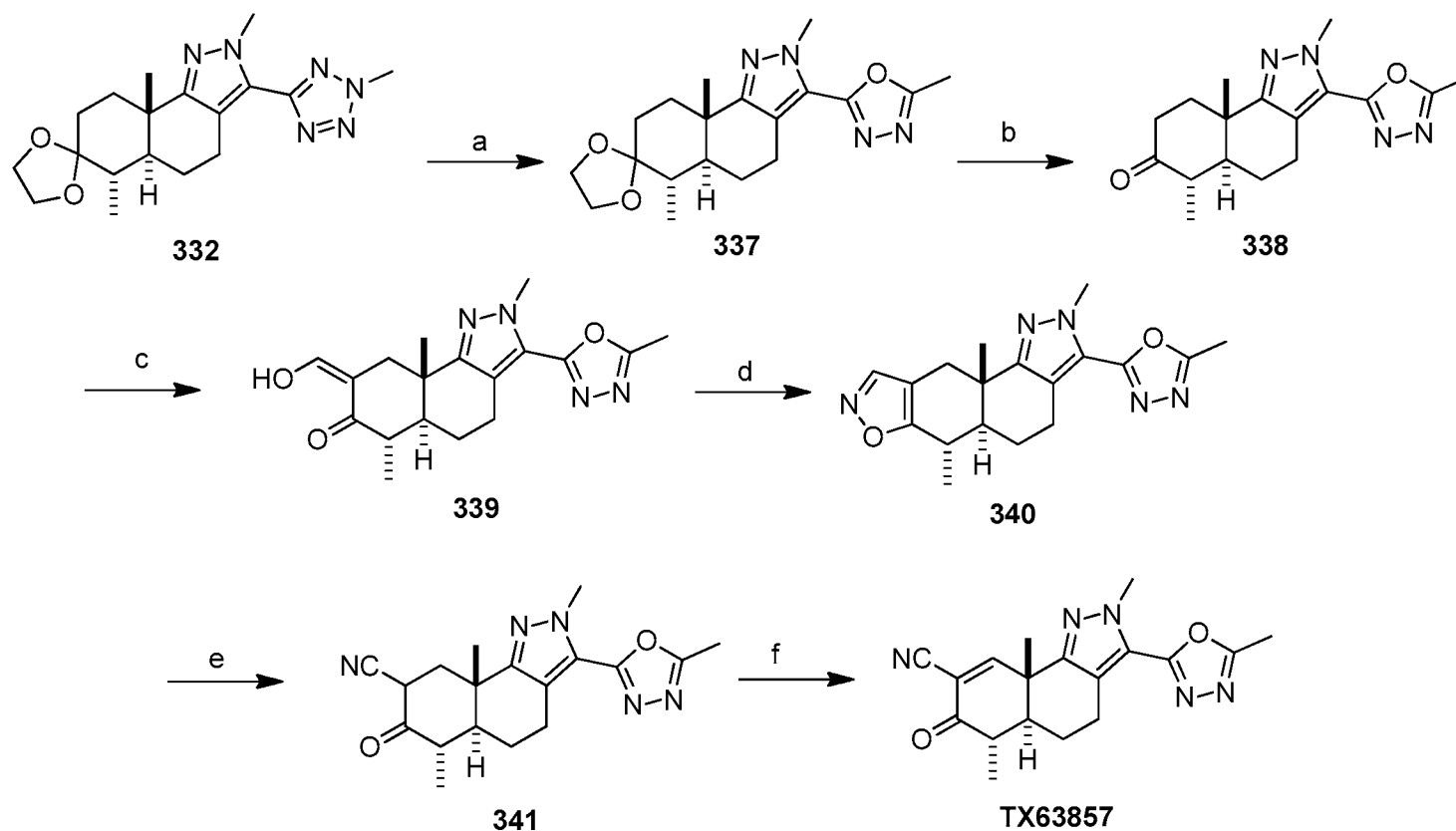
Reagents and conditions pertaining to Schemes 63: (a) $\text{Zn}(\text{CN})_2$, dppf, Na_2CO_3 , $\text{Pd}(\text{OAc})_2$, DMA, 120°C , 16 hr, 90%; (b) HCl (aq), THF, MeOH, 3 day, 99%; (c) HCO_2Et , NaOMe, THF, RT, 16 hr; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, THF, H_2O , 50°C , 16 hr, 100%; (e) NaOMe, THF/MeOH, 50°C , 4 hr, 72%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C to RT, 2 h; (ii) pyridine, 55°C , 5 hr, 74%.

Scheme 64:



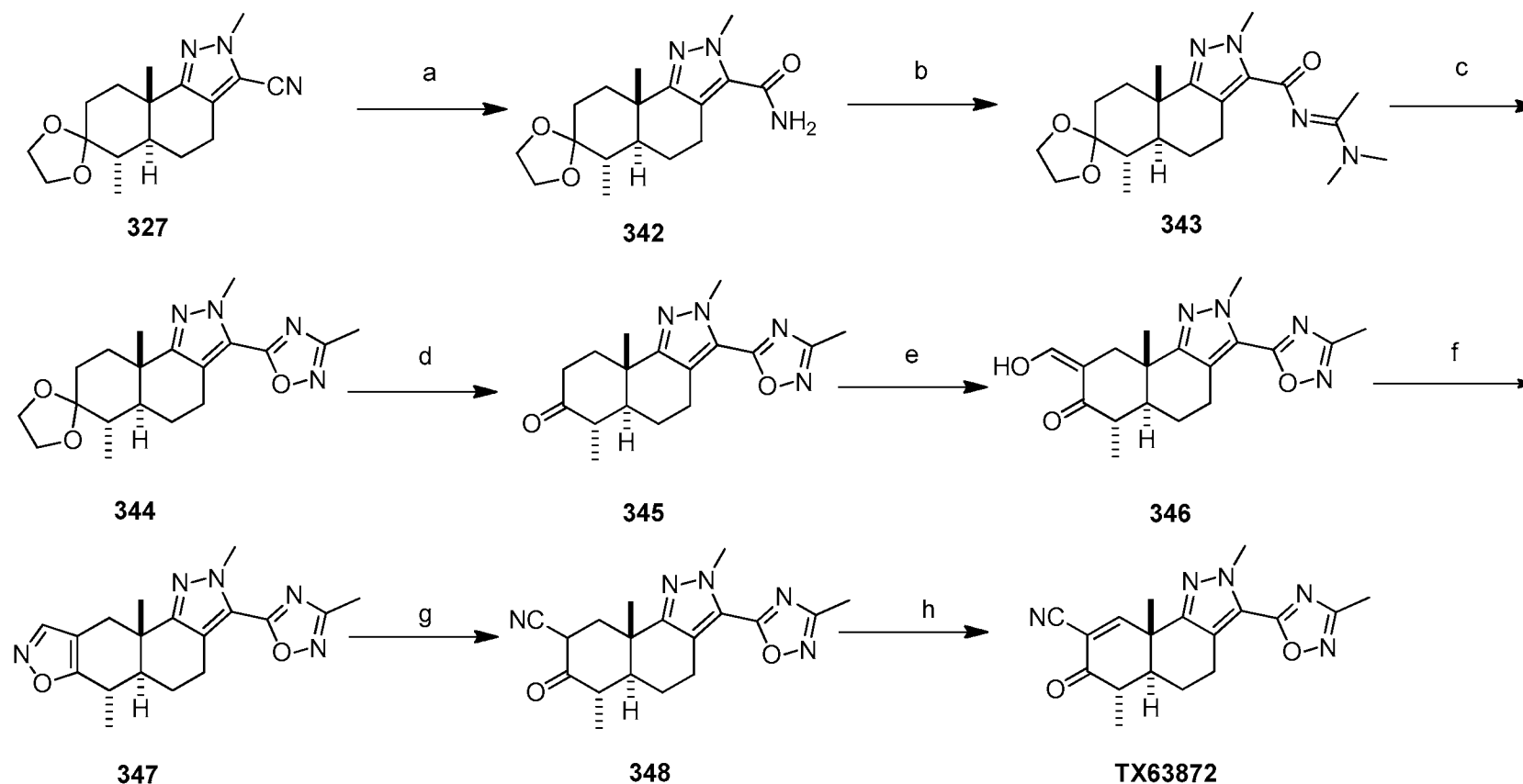
Reagents and conditions pertaining to Schemes 64: (a) TMSN_3 , Bu_2SnO , toluene, 130 °C, 16 hr, 43%; (b) HCl (aq), THF, 16 hr, 97%; (c) HCO_2Et , NaOMe , THF, RT, 16 hr, 100%; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, THF, 50°C, 16 hr, 90%; (e) NaOMe , THF/MeOH, 50 °C, 4 hr, 86%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, 70%.

Scheme 65:



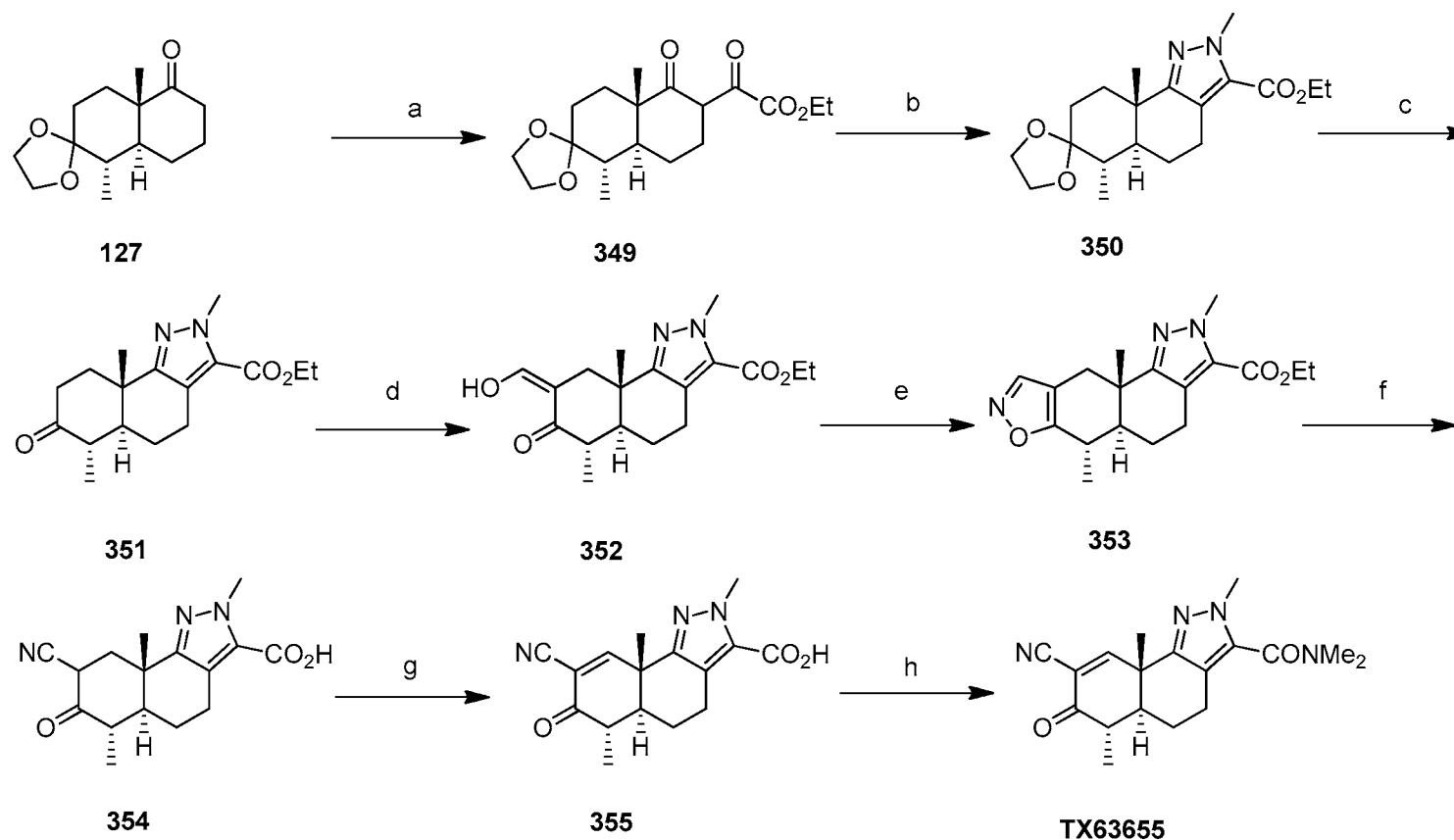
Reagents and conditions pertaining to Schemes 65: (a) Ac_2O , Pyridine, 110°C , 3 hr; (b) HCl (aq), THF, 3 day, 20%; (c) HCO_2Et , NaOMe, THF, RT, 16 hr, 100%; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 50°C , 4 hr, then TsOH , benzene, reflux, 7 hr, 47%; (e) NaOMe, THF/EtOH, 50°C , 4 hr, 100%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C to RT, 2 h; (ii) pyridine, 55°C , 5 hr, 46%.

Scheme 66:



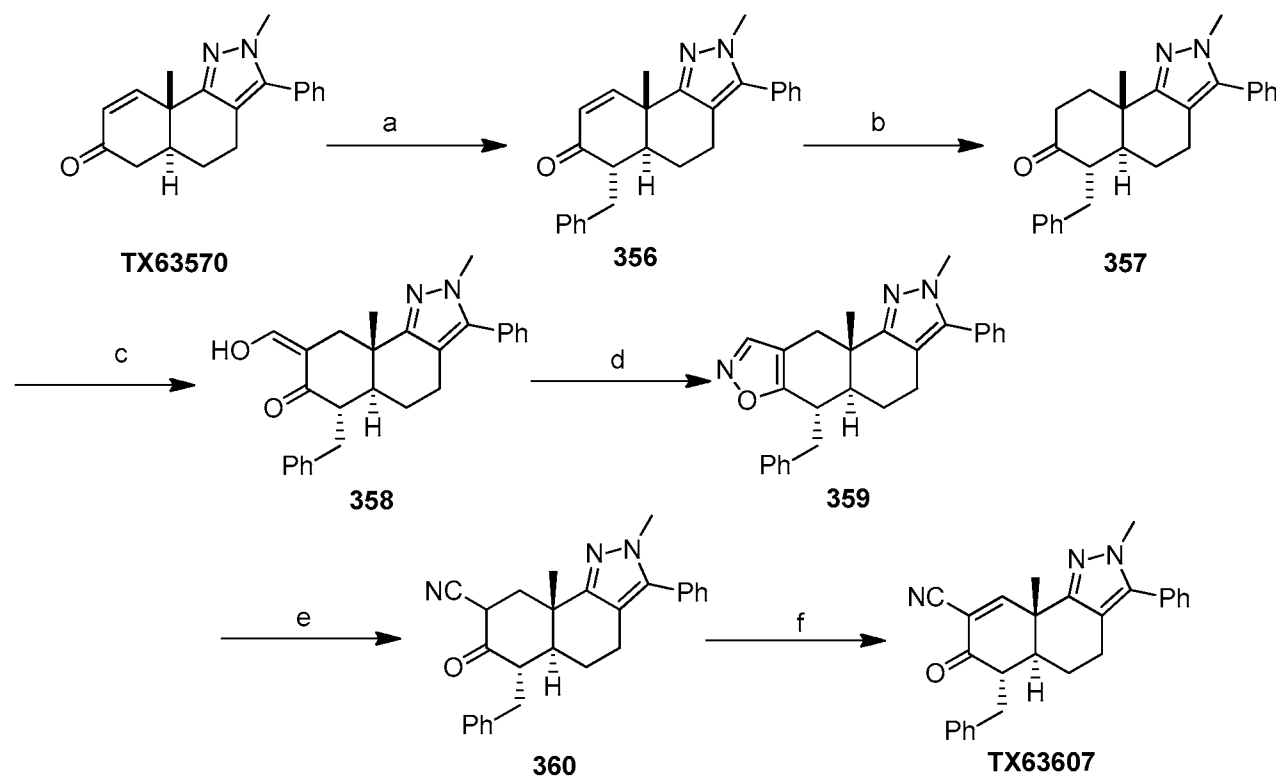
Reagents and conditions pertaining to Schemes 66: (a) KOH, EtOH, H₂O, 4 day, 100%; (b) Dimethylacetamide dimethylacetal, 80 °C, 3 hr; (c) NH₂OH-HCl, TEA, AcOH, 80 °C, 2 hr, 69%; (d) HCl (aq), THF, 4 day, 97%; (e) HCO₂Et, NaOMe, THF, RT, 16 hr, 100%; (f) NH₂OH-HCl, EtOH, 50 °C, 4 hr, then TsOH, benzene, reflux, 7 hr, 100%; (g) NaOMe, THF/EtOH, 50 °C, 4 hr, 77%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, 79%.

Scheme 67:



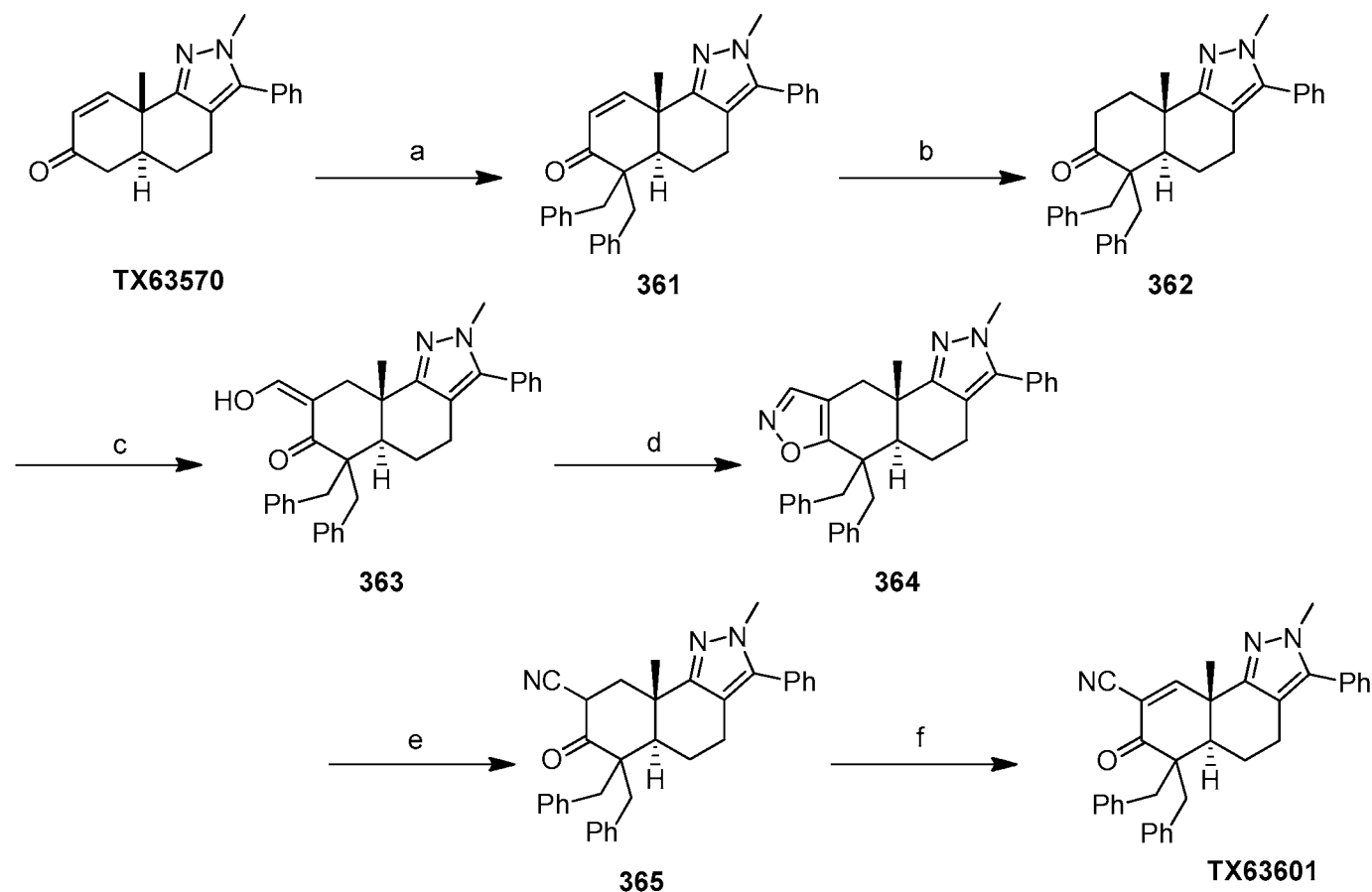
Reagents and conditions pertaining to Schemes 67: (a) Diethyl oxalate, NaH, THF, reflux, 16 hr, 100%; (b) MeNHNH₂, EtOH, 60 °C, 16 hr, 19%; (c) HCl (aq), THF, 16 hr, 73%; (d) HCO₂Et, NaOMe, THF, RT, 16 hr, 100%; (e) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 100%; (f) NaOMe, THF/MeOH, 50 °C, 6 hr, 100%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 55 °C, 5 hr, 80%; (h) (COCl)₂, THF, RT, 3 hr, 35%.

Scheme 68:



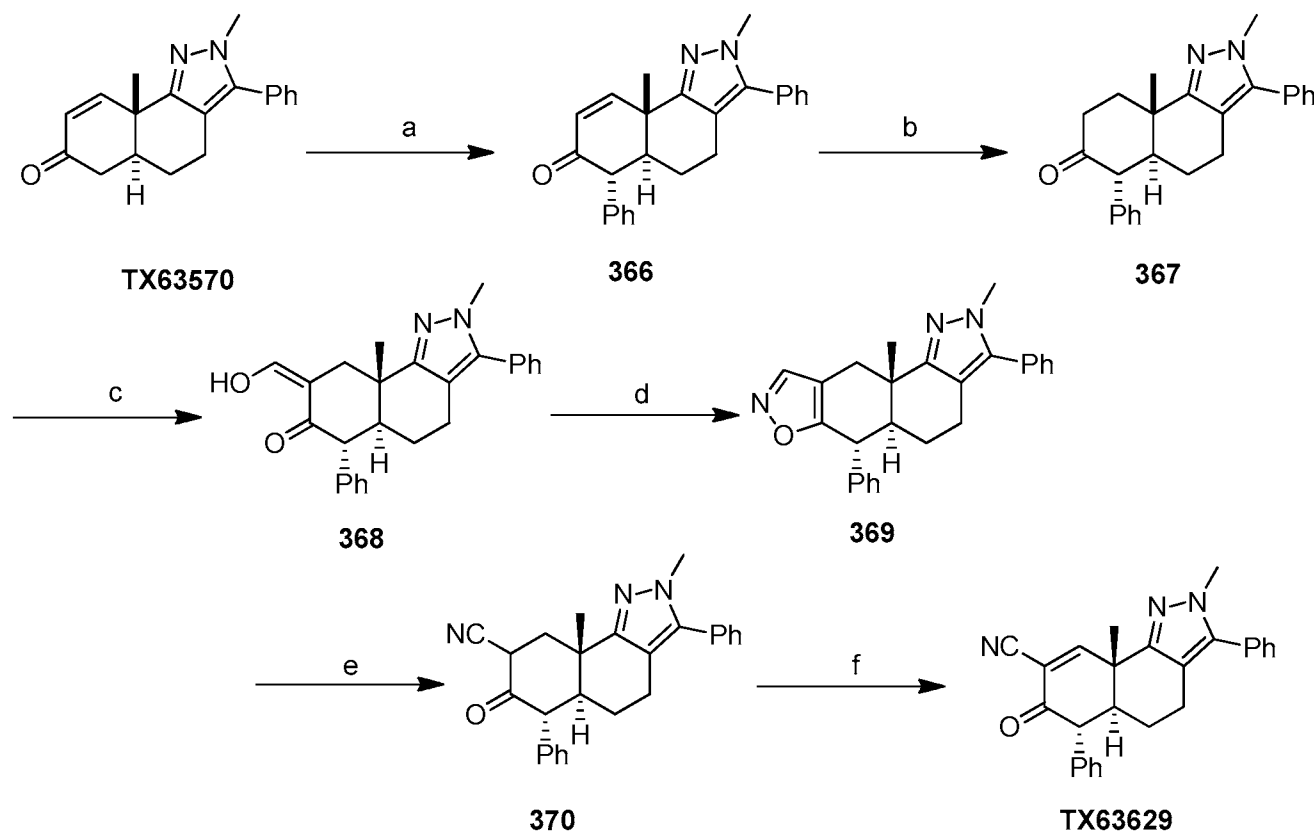
Reagents and conditions pertaining to Schemes 68: (a) n-BuLi, DIPA, BnBr, THF, -78 °C to RT, 45%; (b) H₂, Pd/C, THF, 48 hr; (c) HCO₂Et, NaOMe, THF, RT, 16 hr, 98%; (d) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 100%; (e) NaOMe, THF/MeOH, 50 °C, 9 hr, 100%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr, 39%.

Scheme 69:



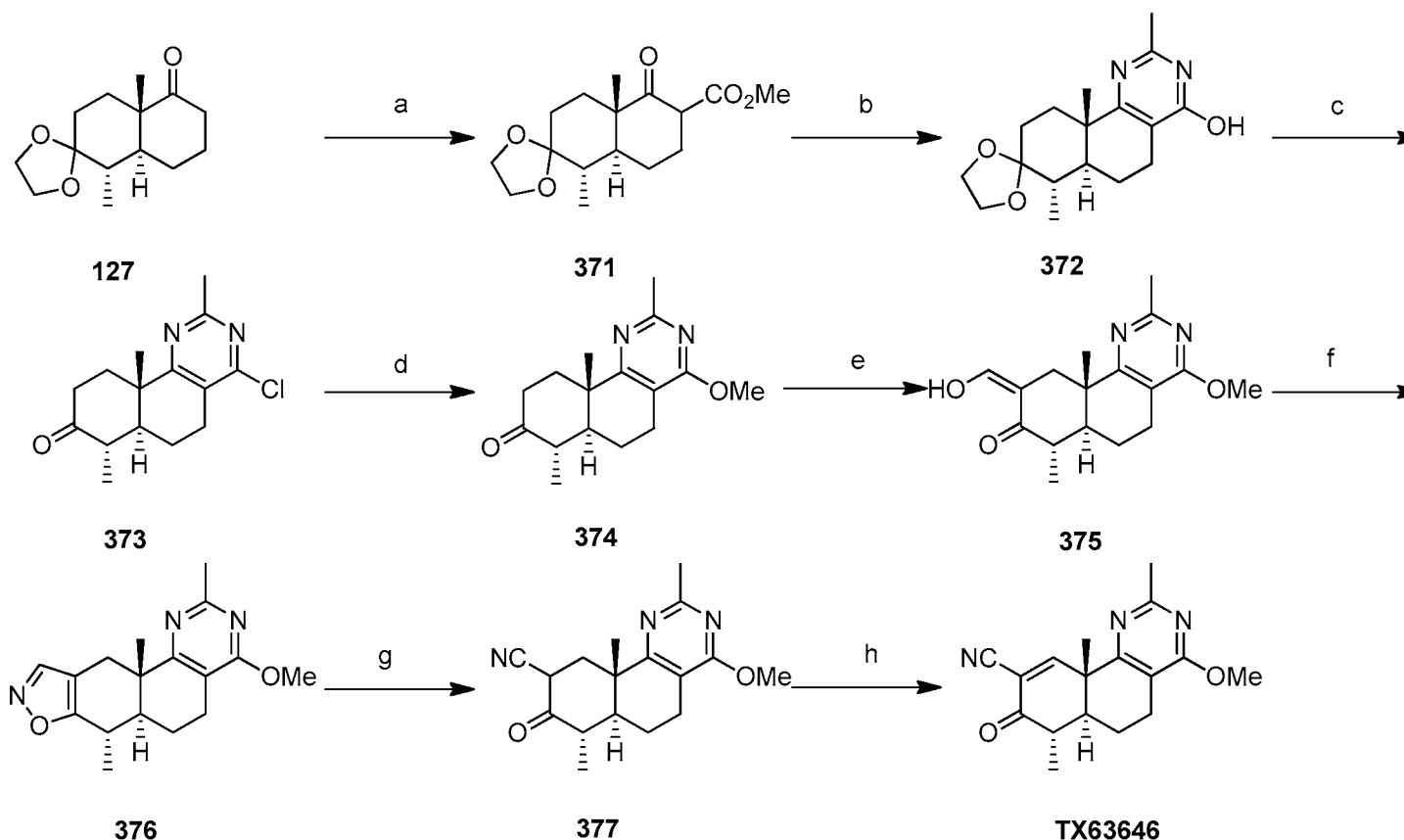
Reagents and conditions pertaining to Schemes 69: (a) KHMDS, THF, BnBr, -60 °C to RT, 15%; (b) H₂, Pd/C, THF, 48 hr; (c) HCO₂Et, NaOMe, THF, RT, 16 hr, 95%; (d) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 100%; (e) NaOMe, THF/MeOH, 50 °C, 9 hr, 98%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr, 28%.

Scheme 70:



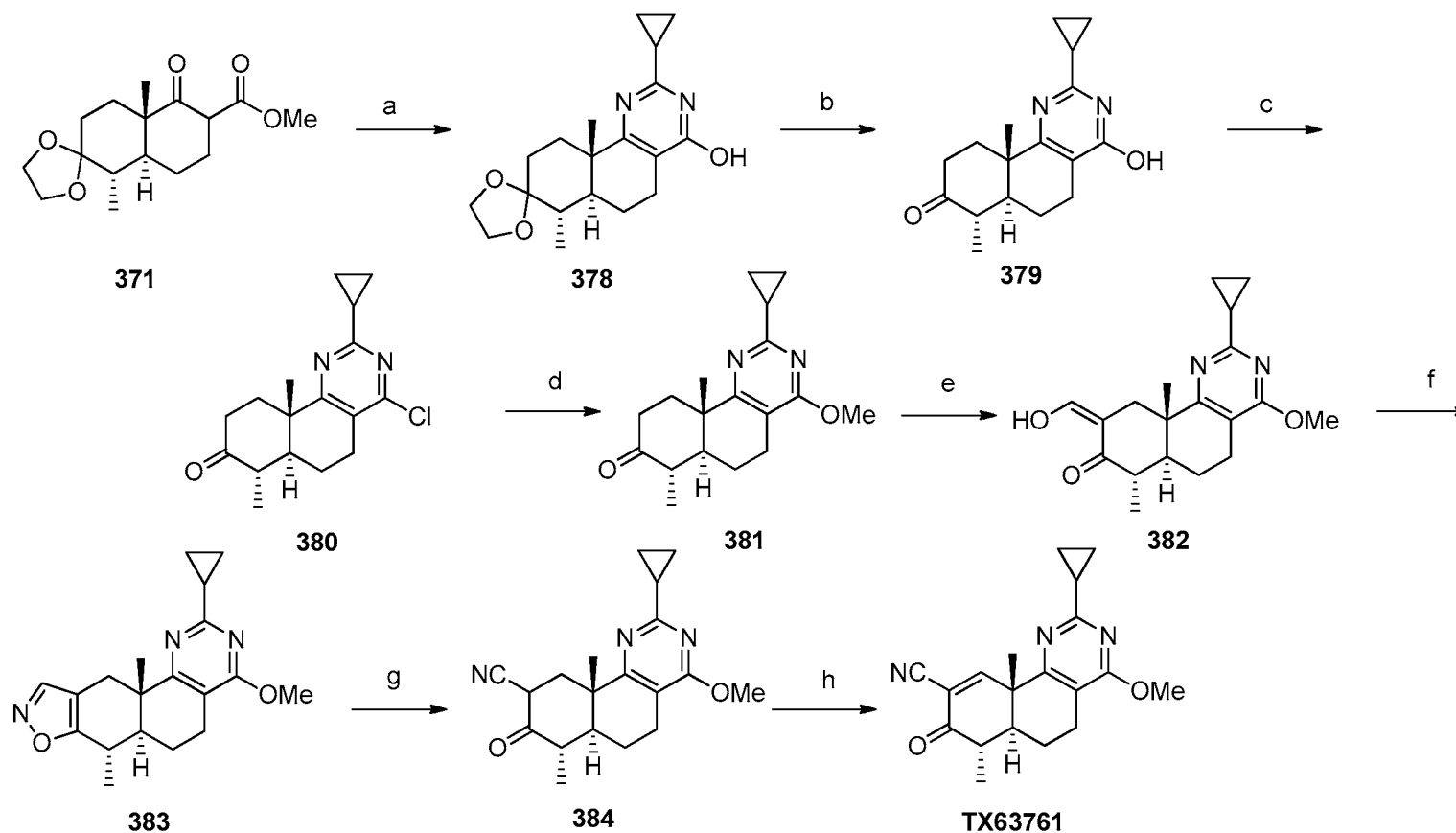
Reagents and conditions pertaining to Schemes 70: (a) DIPA, n-BuLi, THF, Ph_2ICl , -78°C to RT, 31%; (b) H_2 , Pd/C, THF, 48 hr; (c) HCO_2Et , NaOMe, THF, RT, 16 hr; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 50°C , 16 hr; (e) NaOMe, THF/MeOH, 50°C , 9 hr, 91%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0°C to RT, 2 h; (ii) pyridine, 60°C , 4 hr, 79%.

Scheme 71:



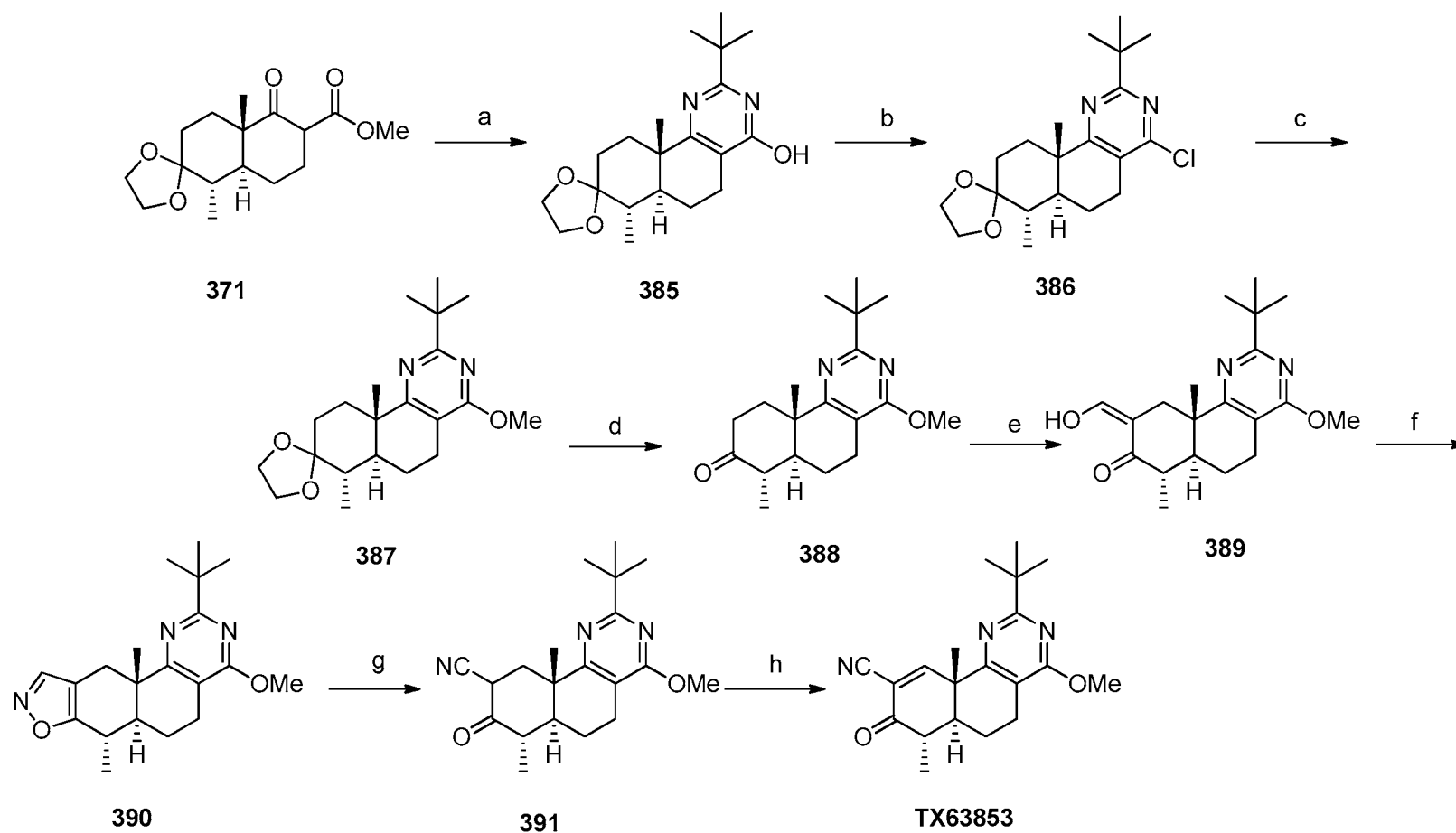
Reagents and conditions pertaining to Schemes 71: (a) Dimethyl carbonate, NaH, THF, reflux, 16 hr; (b) Acetimidamide hydrochloride, piperidine, iPrOH, reflux, 48 hr, 42%; (c) POCl₃, DMF, 140 °C, 3 hr, 100%; (d) NaOMe, MeOH, 50 °C, 3 hr, 44%; (e) HCO₂Et, NaOMe, THF, RT, 16 hr, 100%; (f) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 100%; (g) NaOMe, THF/MeOH, 50 °C, 9 hr, 100%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr, 30%.

Scheme 72:



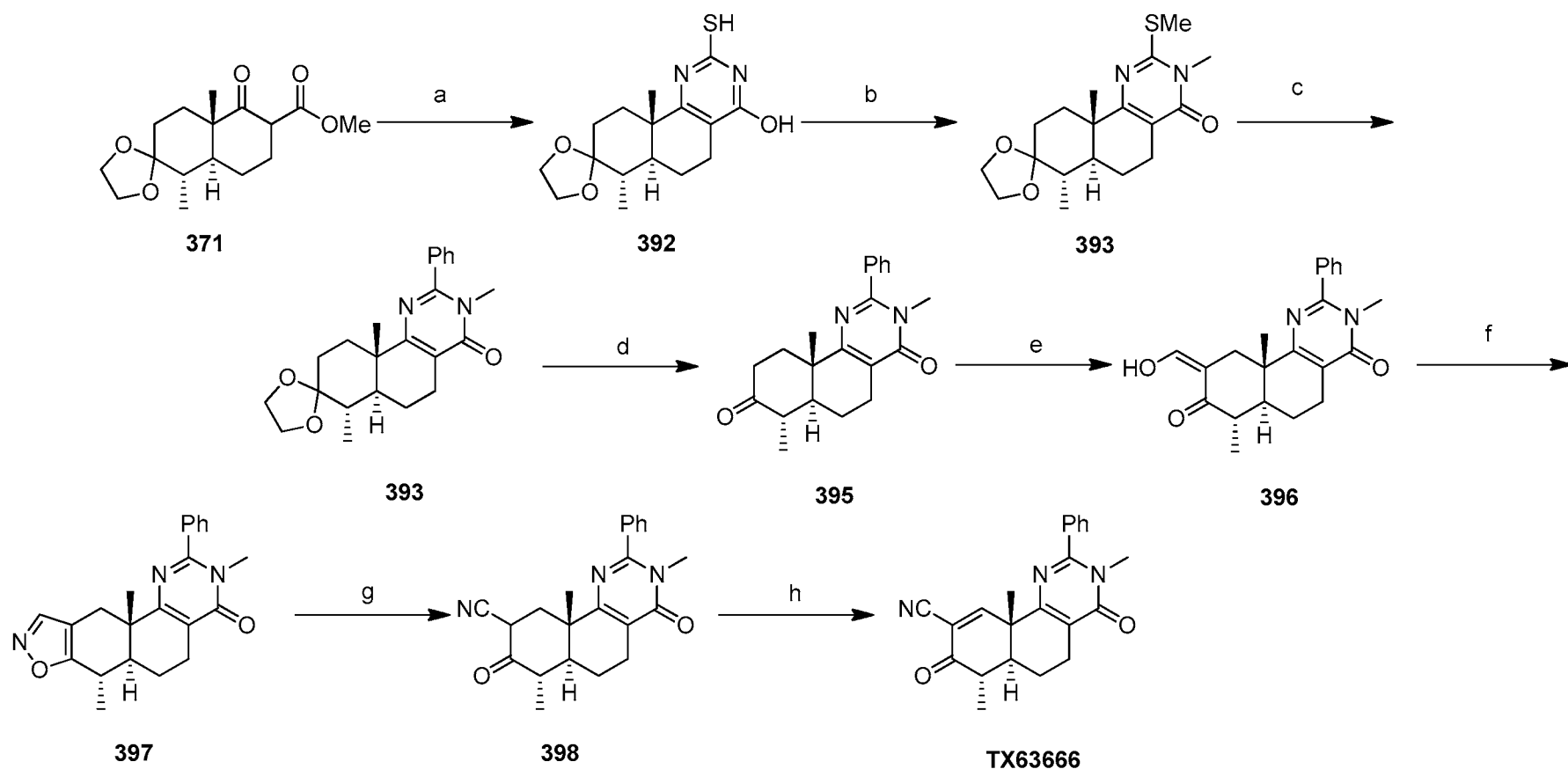
Reagents and conditions pertaining to Schemes 72: (a) Cyclopropanecarboximidamide hydrochloride, piperidine, iPrOH, 90 °C, 72 hr, 77%; (b) HCl (aq), MeOH, iPrOH, RT, 16 hr, 94%; (c) POCl₃, DIPEA, benzene, 80 °C, 16 hr, 94%; (d) NaOMe, MeOH, 50 °C, 2 hr, 100%; (e) HCO₂Et, NaOMe, THF, RT, 16 hr, 100%; (f) NH₂OH-HCl, EtOH, 50 °C, 2 hr, then RT, 16 hr, 90%; (g) NaOMe, MeOH, RT, 16 hr, 41%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 3 hr, 23%.

Scheme 73:



Reagents and conditions pertaining to Schemes 73: (a) 2,2-dimethylpropionamidine hydrochloride, piperidine, nBuOH, 100 °C, 72 hr, 60%; (b) POCl₃, DIPEA, benzene, 90 °C, 2 hr then RT, 16 hr, 93%; (c) NaOMe, MeOH, 50 °C, 2 hr, 100%; (d) HCl (aq), MeOH, iPrOH, RT, 16 hr, 92%; (e) HCO₂Et, NaOMe, MeOH, RT, 16 hr, 97%; (f) NH₂OH-HCl, EtOH, 50 °C, 2 hr, then RT, 16 hr, 100%; (g) NaOMe, MeOH, RT, 16 hr, 50%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 2 hr, 38%.

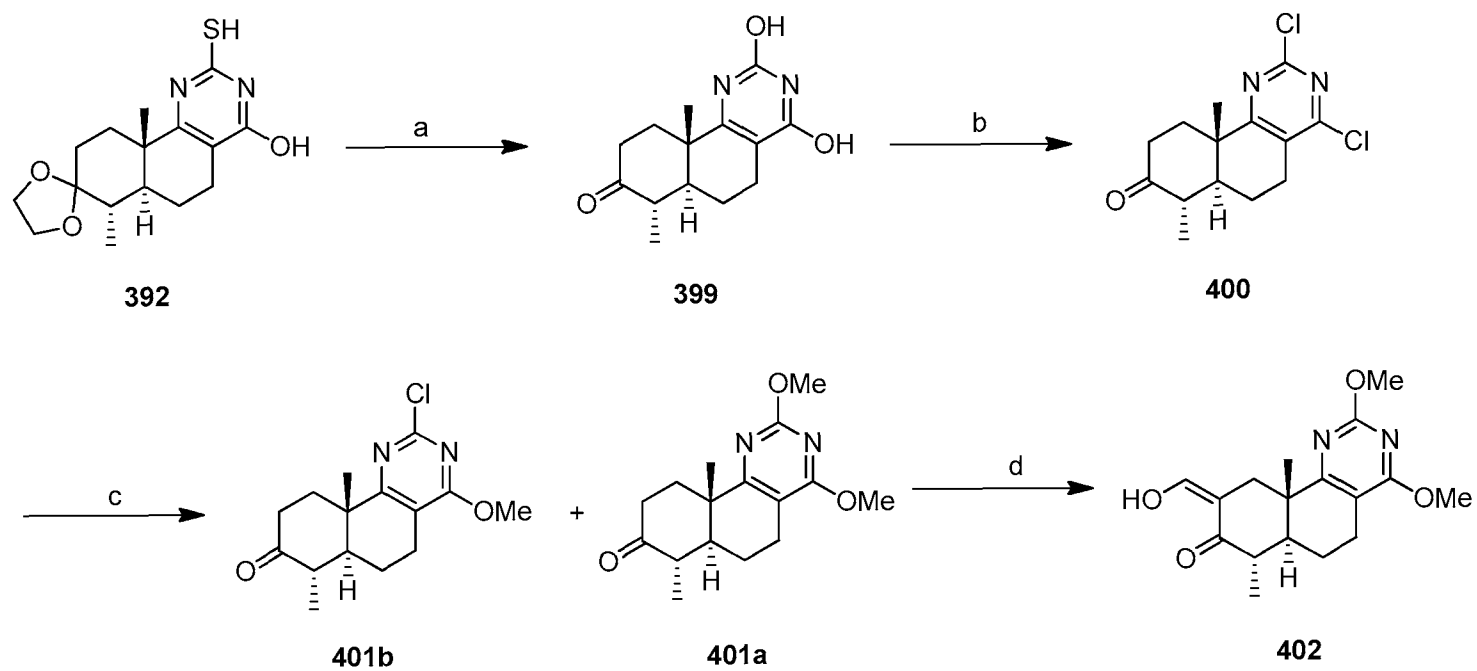
Scheme 74:



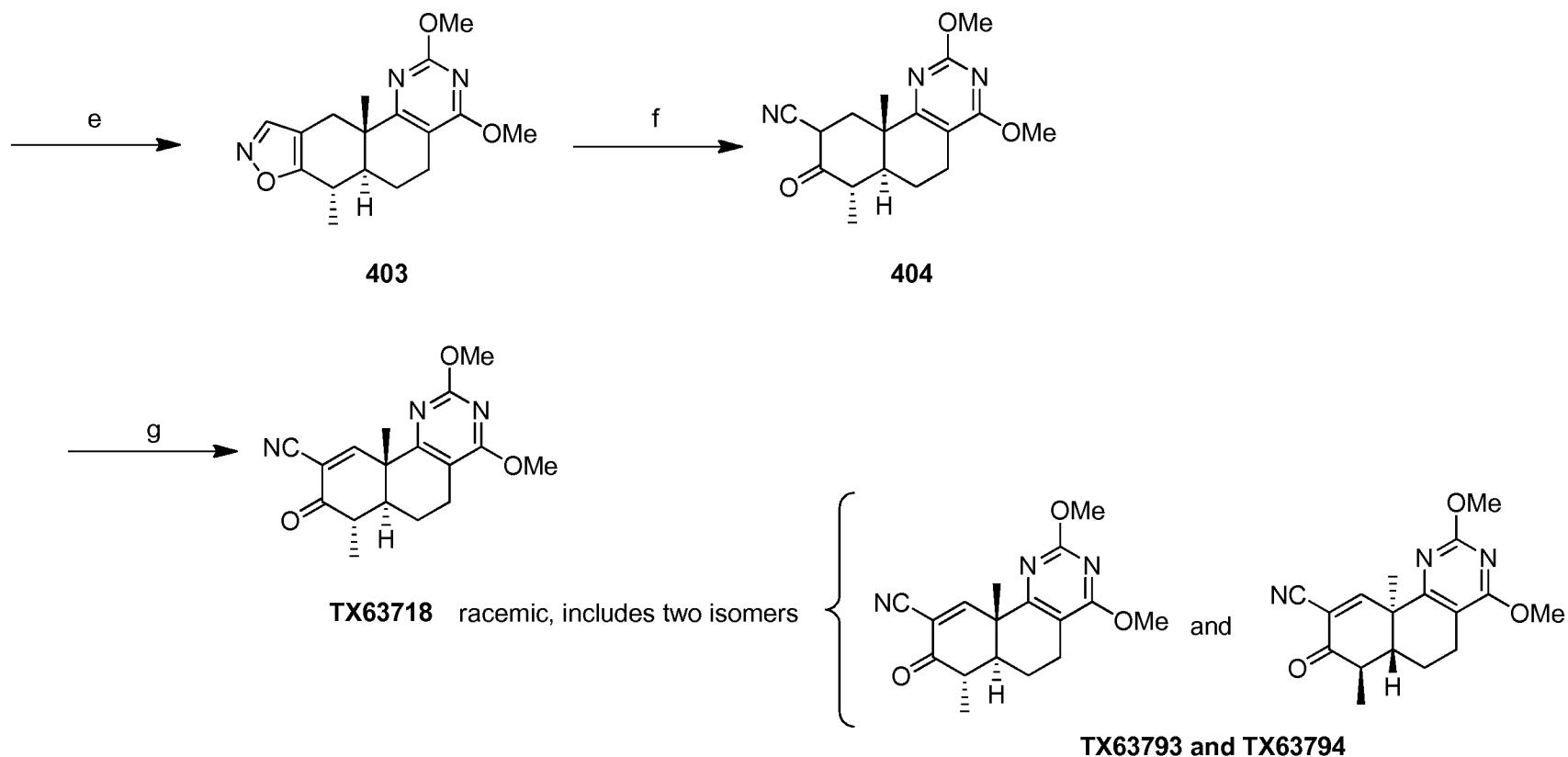
Reag

ents and conditions pertaining to Schemes 74: (a) Thiourea, KO-tBu, EtOH, reflux, 16 hr, 87%; (b) MeI, K₂CO₃, DMF, RT, 2 hr, 100%; (c) PhB(OH)₂, Pd(PPh₃)₄, Cu(I) thiophene 2-carboxylate, THF, reflux, 16 hr, 40%; (d) HCl (aq), MeOH, iPrOH, RT, 16 hr, 100%; (e) HCO₂Et, NaOMe, MeOH, RT, 16 hr, 100%; (f) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 98%; (g) NaOMe, THF, MeOH, 50 °C, 16 hr, 50%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr, 62%.

Scheme 75 (a):

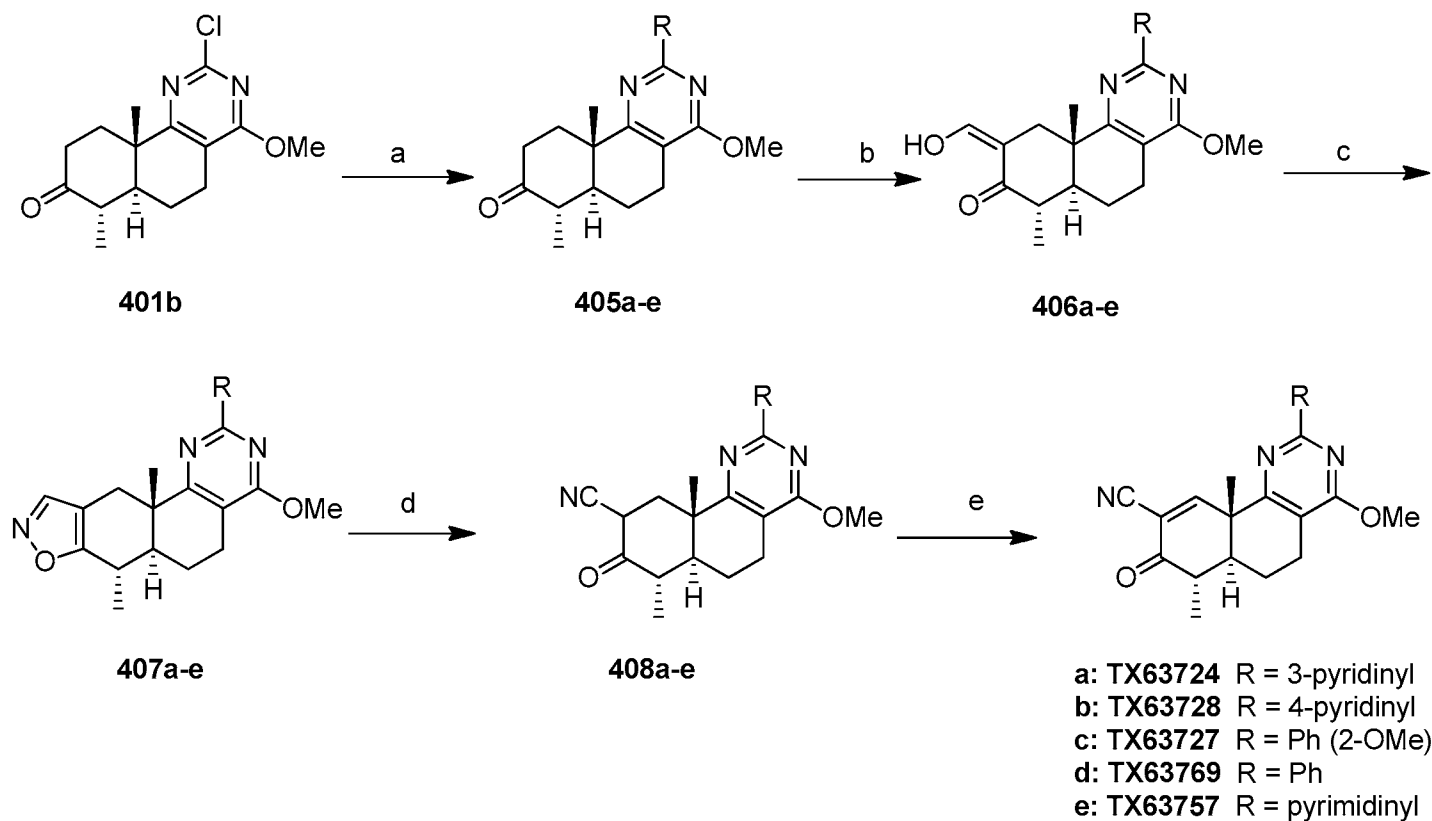


Scheme 75 (b):



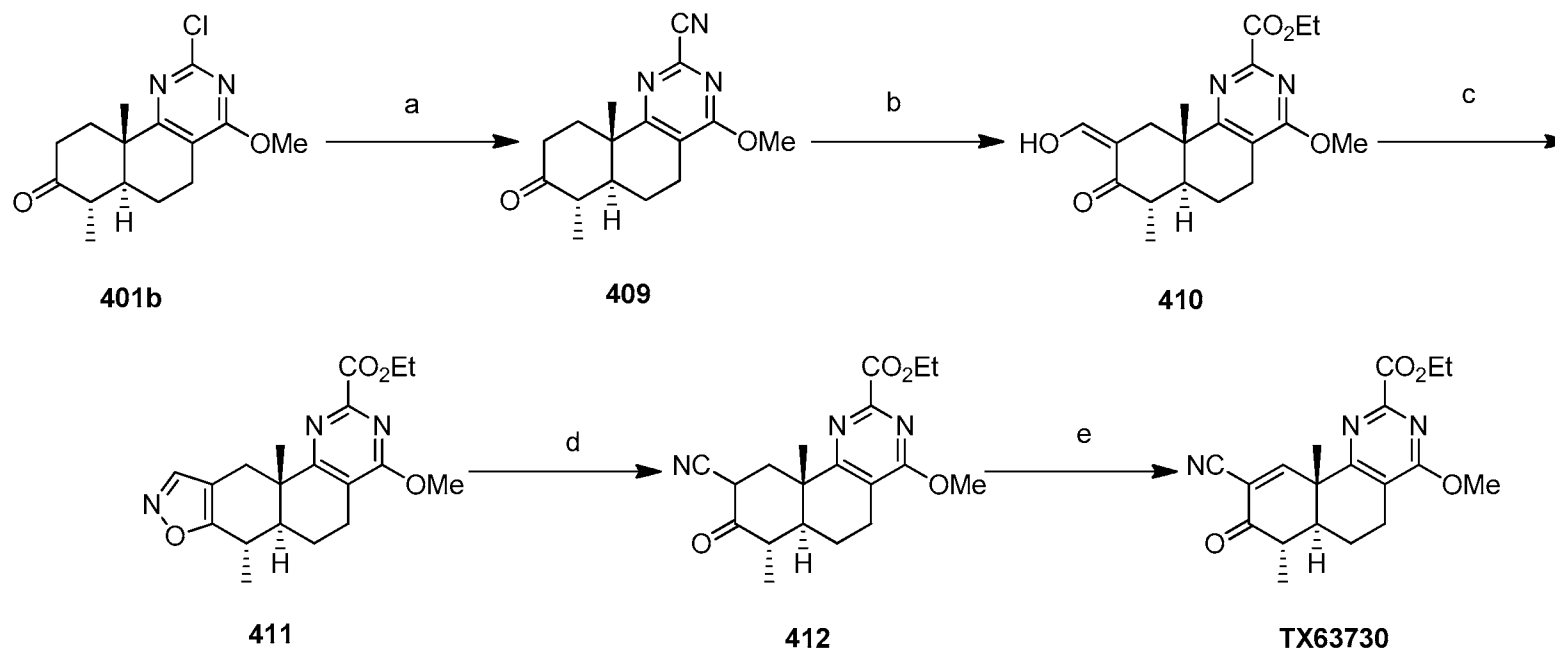
Reagents and conditions pertaining to Schemes 75 (a) and (b): (a) ClCH_2COOH , HCl , H_2O , 100°C , 6 hr, 93%; (b) POCl_3 , DIPEA, 90°C , 16 hr, 90%; (c) NaOMe , MeOH , 50°C , 1 hr, **401a**: 65%, **401b**: 5.5%; (d) HCO_2Et , NaOMe , MeOH , RT, 16 hr, 100%; (e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH , 50°C , 16 hr, 100%; (f) NaOMe , THF , MeOH , 50°C , 6 hr, 100%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF , 0°C to RT, 2 h; (ii) pyridine, 50°C , 16 hr, 40%.

Scheme 76:



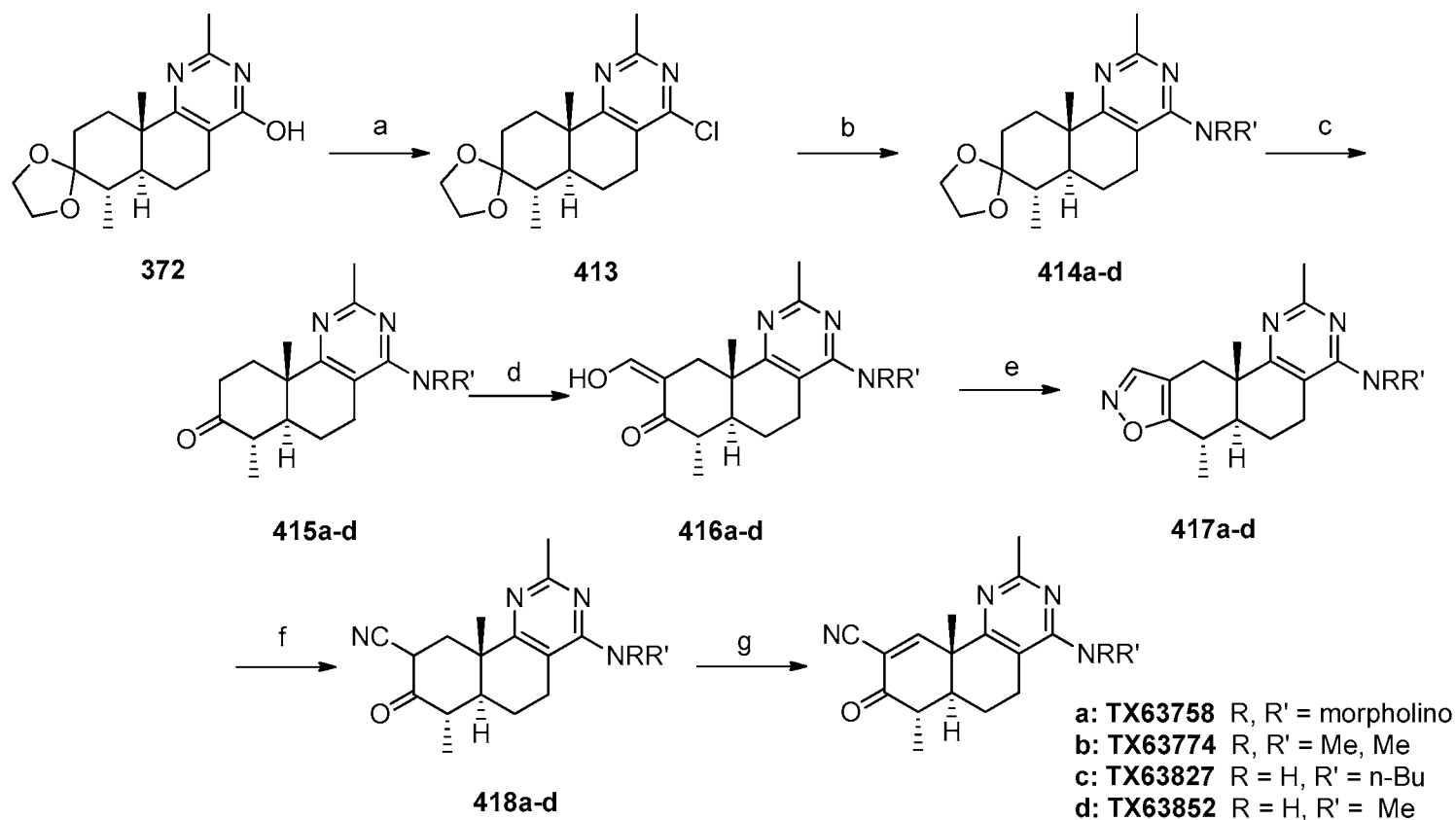
Reagents and conditions pertaining to Schemes 76: (a) R-B(OH)₂, PPh₃, K₃PO₄, Pd(OAc)₂, DMF, DME, 90 °C, 16 hr; (b) HCO₂Et, NaOMe, MeOH, RT, 16 hr; (c) NH₂OH-HCl, EtOH, 50 °C, 16 hr; (d) NaOMe, THF, MeOH, 50 °C, 16 hr; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr.

Scheme 77:



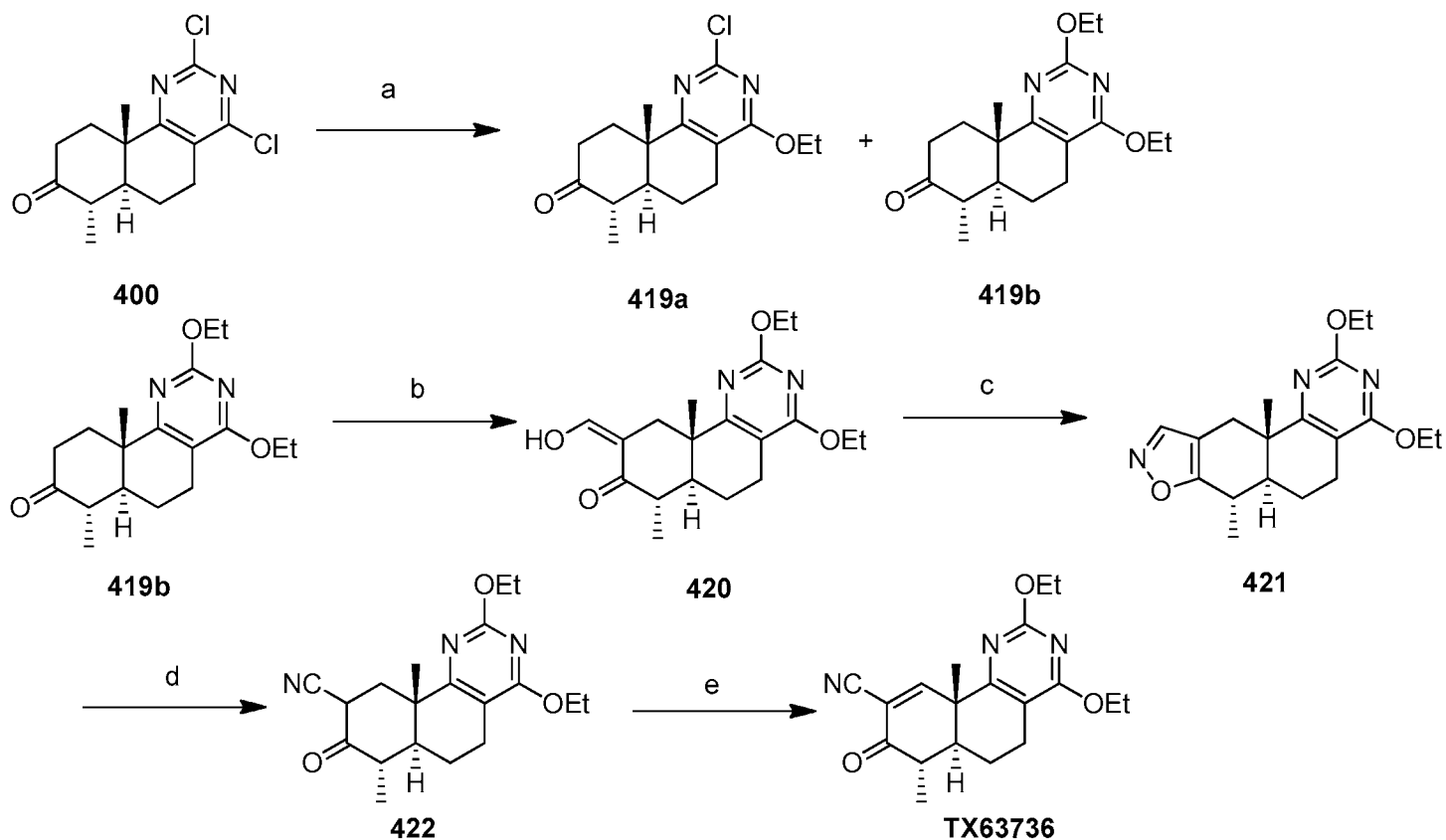
Reagents and conditions pertaining to Schemes 77: (a) $\text{Zn}(\text{CN})_2$, dppf, Na_2CO_3 , DMAc, 120 °C, 16 hr, 40%; (b) HCO_2Et , NaOMe, MeOH, RT, 16 hr; (c) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 50 °C, 16 hr, 30%; (d) TEA, MeCN, 85 °C, 16 hr; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr, 41%.

Scheme 78:



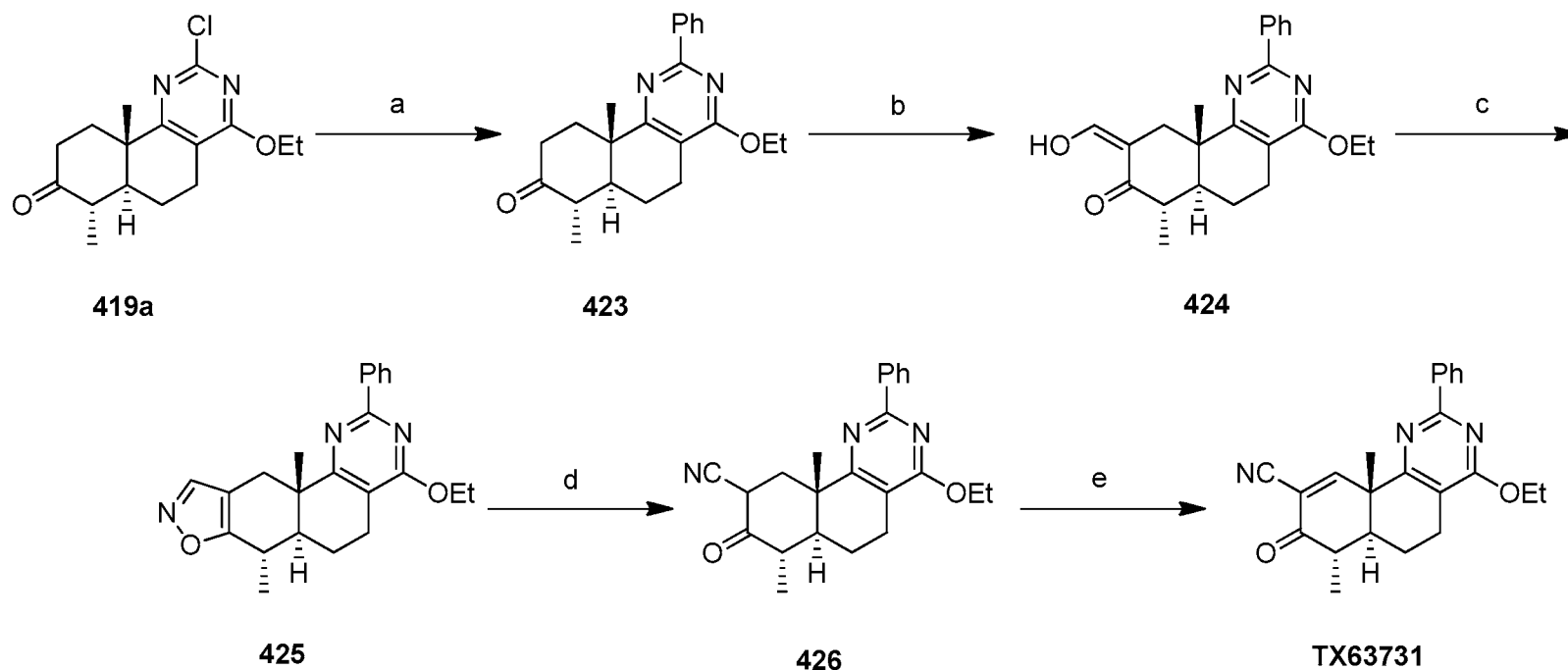
Reagents and conditions pertaining to Schemes 78: (a) POCl₃, DIPEA, benzene, 90 °C, 4 hr; (b) RR'NH, DIPEA, iPrOH, 90 °C, 48 hr; (c) HCl (aq), MeOH, RT, 16 hr (d) HCO₂Et, NaOMe, MeOH, RT, 16 hr; (e) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 30%; (f) NaOMe, THF, MeOH, 50 °C, 16 hr; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr.

Scheme 79:



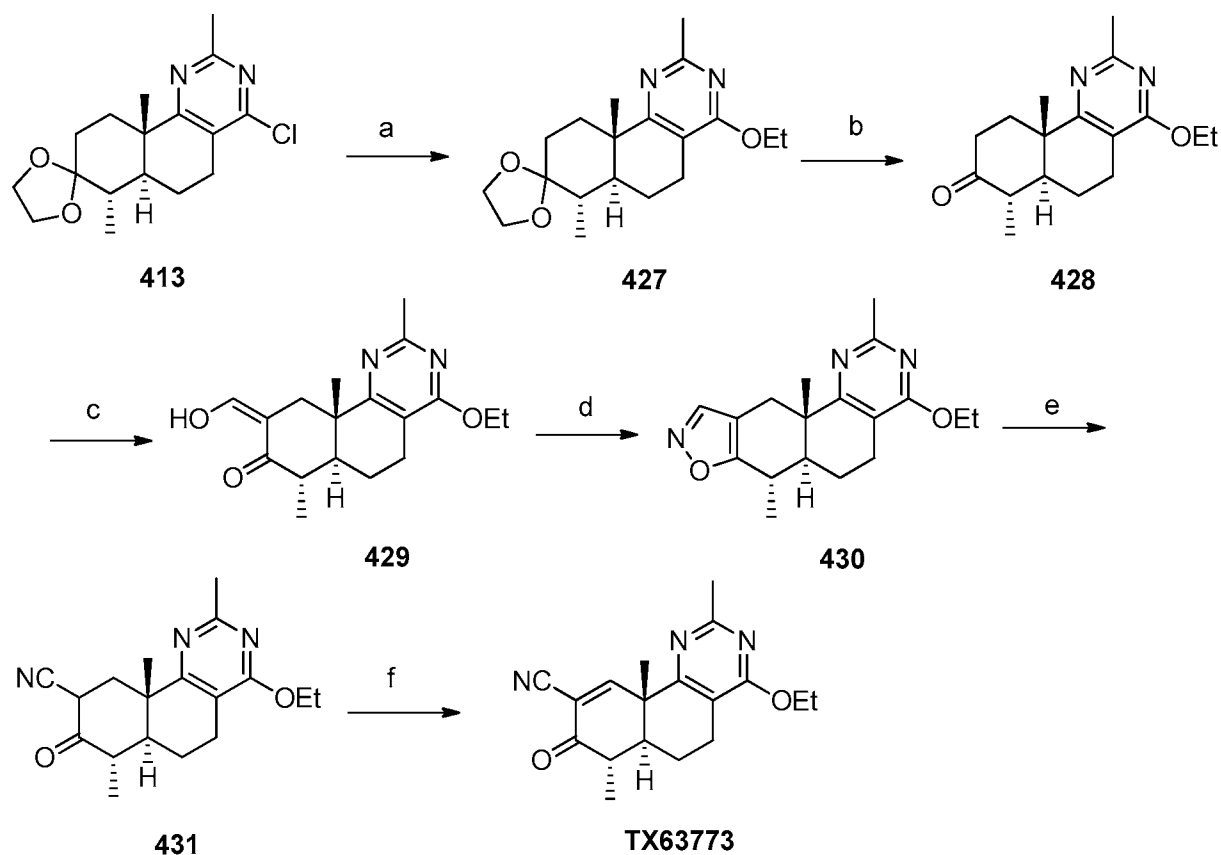
Reagents and conditions pertaining to Schemes 79: (a) Na, EtOH, 50 °C, 3 hr, 35%; (b) HCO₂Et, Na, EtOH, RT, 16 hr, 92%; (c) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 30%; (d) NaOMe, THF, MeOH, 50 °C, 16 hr; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr, 12%.

Scheme 80:



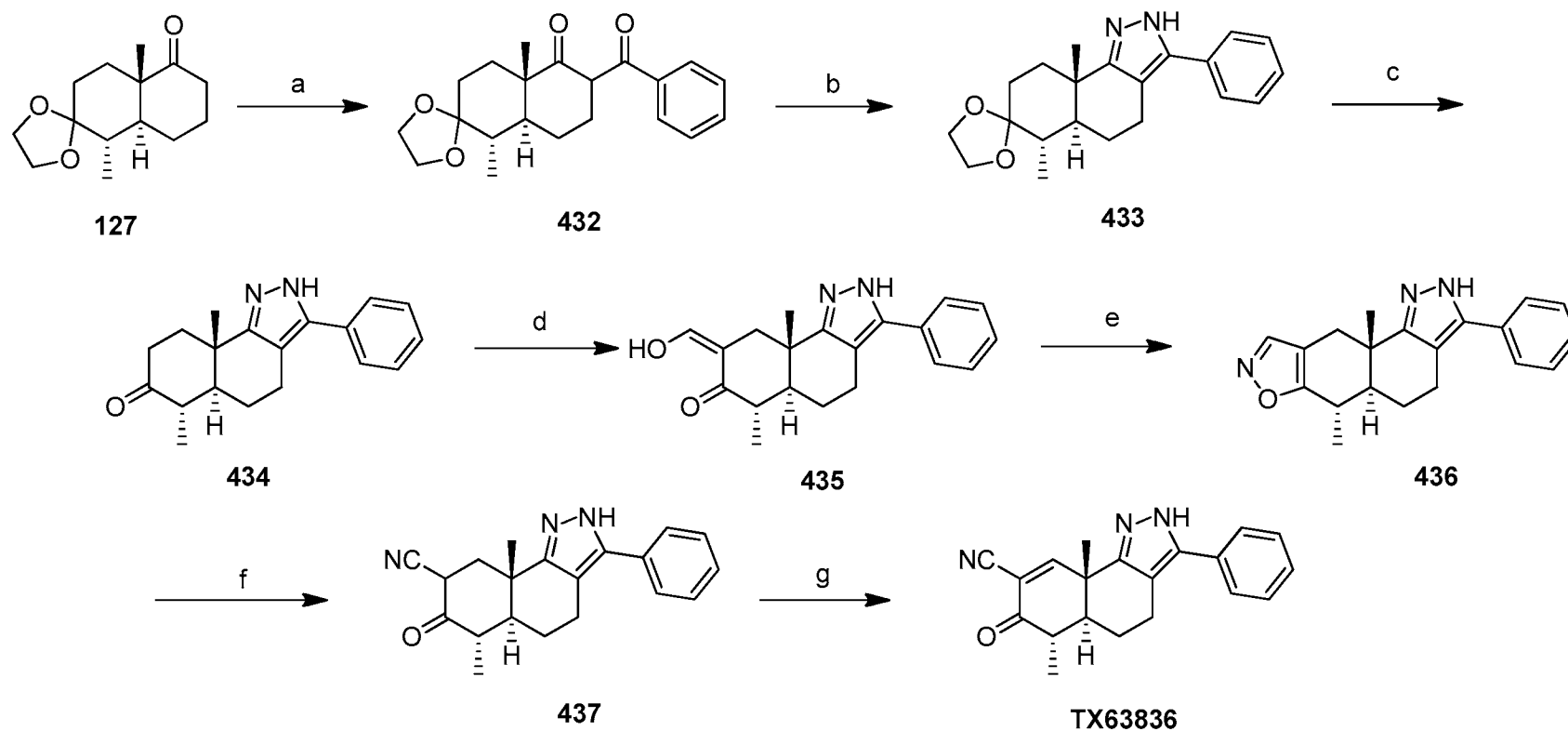
Reagents and conditions pertaining to Schemes 80: (a) PhB(OH)_2 , PPh_3 , K_3PO_4 , Pd(OAc)_2 , DMF, DME, 90 °C, 16 hr, 67%; (b) HCO_2Et , NaOMe, MeOH, RT, 16 hr; (c) $\text{NH}_2\text{OH-HCl}$, EtOH, 50 °C, 16 hr; (d) NaOMe, THF, MeOH, 50 °C, 16 hr; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 16 hr, 69%.

Scheme 81:

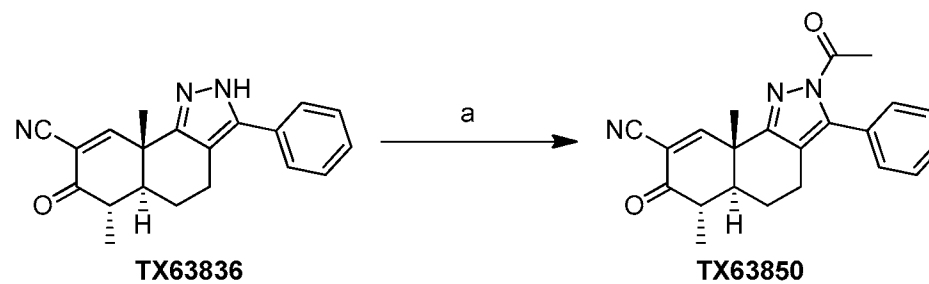


Reagents and conditions pertaining to Schemes 81: (a) EtONa, EtOH, RT, 16 hr; (b) HCl (aq), MeOH, RT, 16 hr, 84%; (c) HCO₂Et, NaOEt, EtOH, Benzene, RT, 16 hr, 96%; (d) NH₂OH-HCl, EtOH, 50 °C, 2 hr then RT, 16 hr; (e) NaOEt, EtOH, MeOH, RT, 16 hr; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 1 h; (ii) pyridine, 50 °C, 2 hr, 48%.

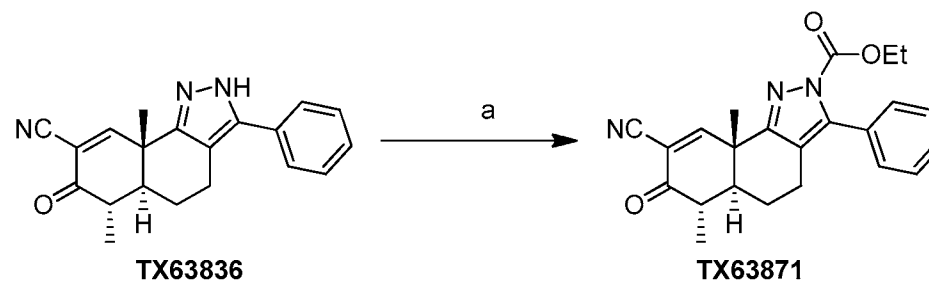
Scheme 82:



Reagents and conditions pertaining to Schemes 82: (a) $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, DIPEA, DCM, then BzCl , RT, 16 hr, 27%; (b) $\text{NHNH}_2 \cdot \text{H}_2\text{O}$, EtOH, 65 °C, 1 hr then RT 5 day; (c) HCl (aq), MeOH, RT, 16 hr; (d) HCO_2Et , NaOMe, MeOH, RT, 16 hr; (e) $\text{NH}_2\text{OH} \cdot \text{HCl}$, EtOH, H_2O , RT, 16 hr, 34%; (f) NaOMe, MeOH, THF, RT, 16 hr; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 3 hr, 43%.

Scheme 83:

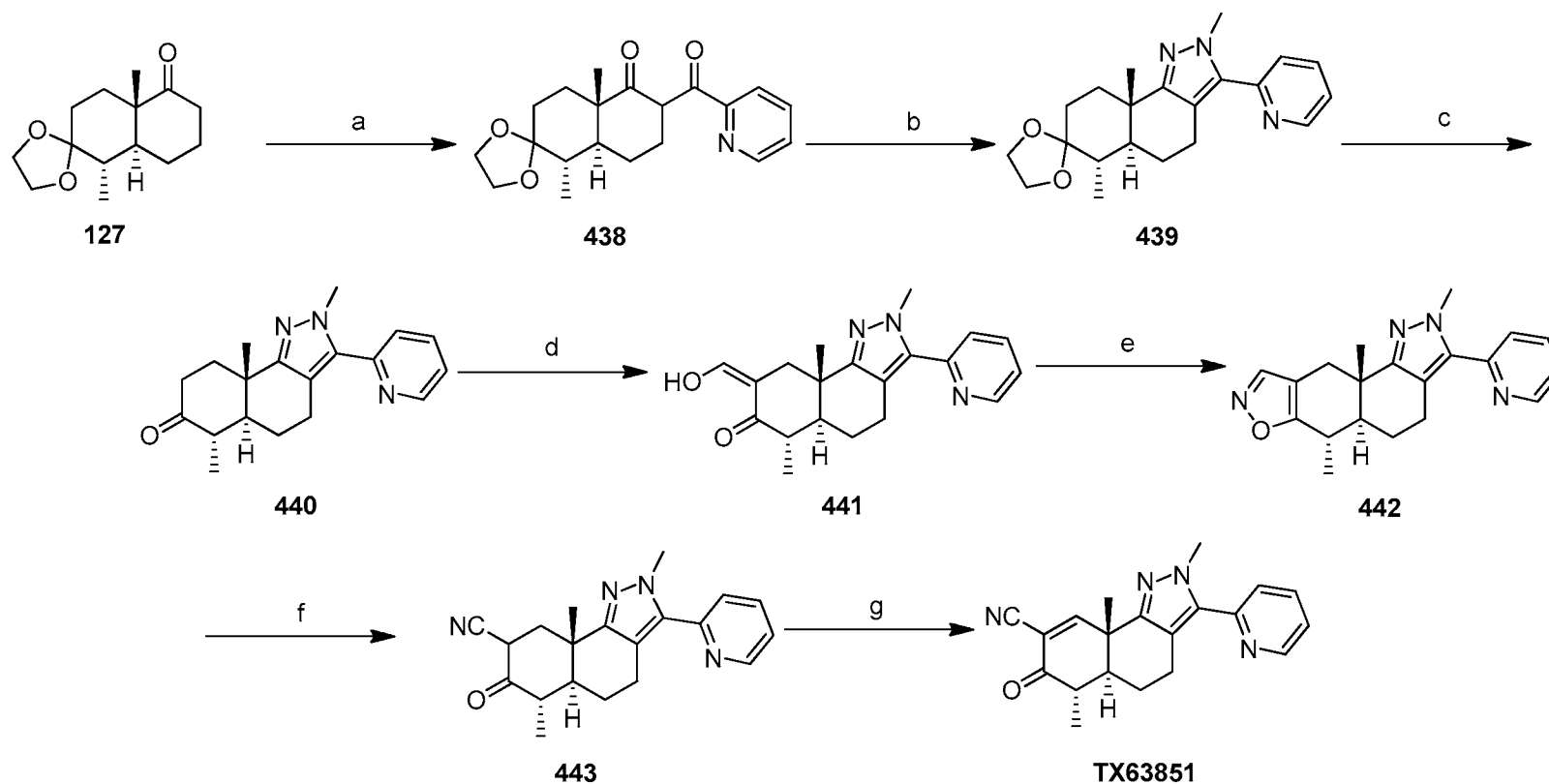
Reagents and conditions pertaining to Schemes 83: (a) Ac_2O , NaOAc , RT, 3 days, 31%.

Scheme 84:

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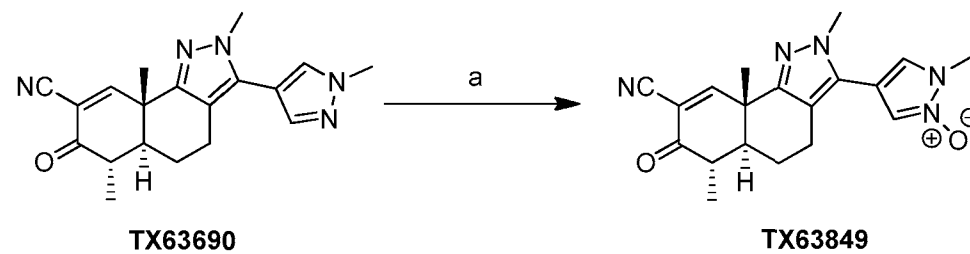
Reagents and conditions pertaining to Schemes 84: (a) Ethyl chloroformate, NaHCO_3 , RT, 16 hr, 76%.

Scheme 85:



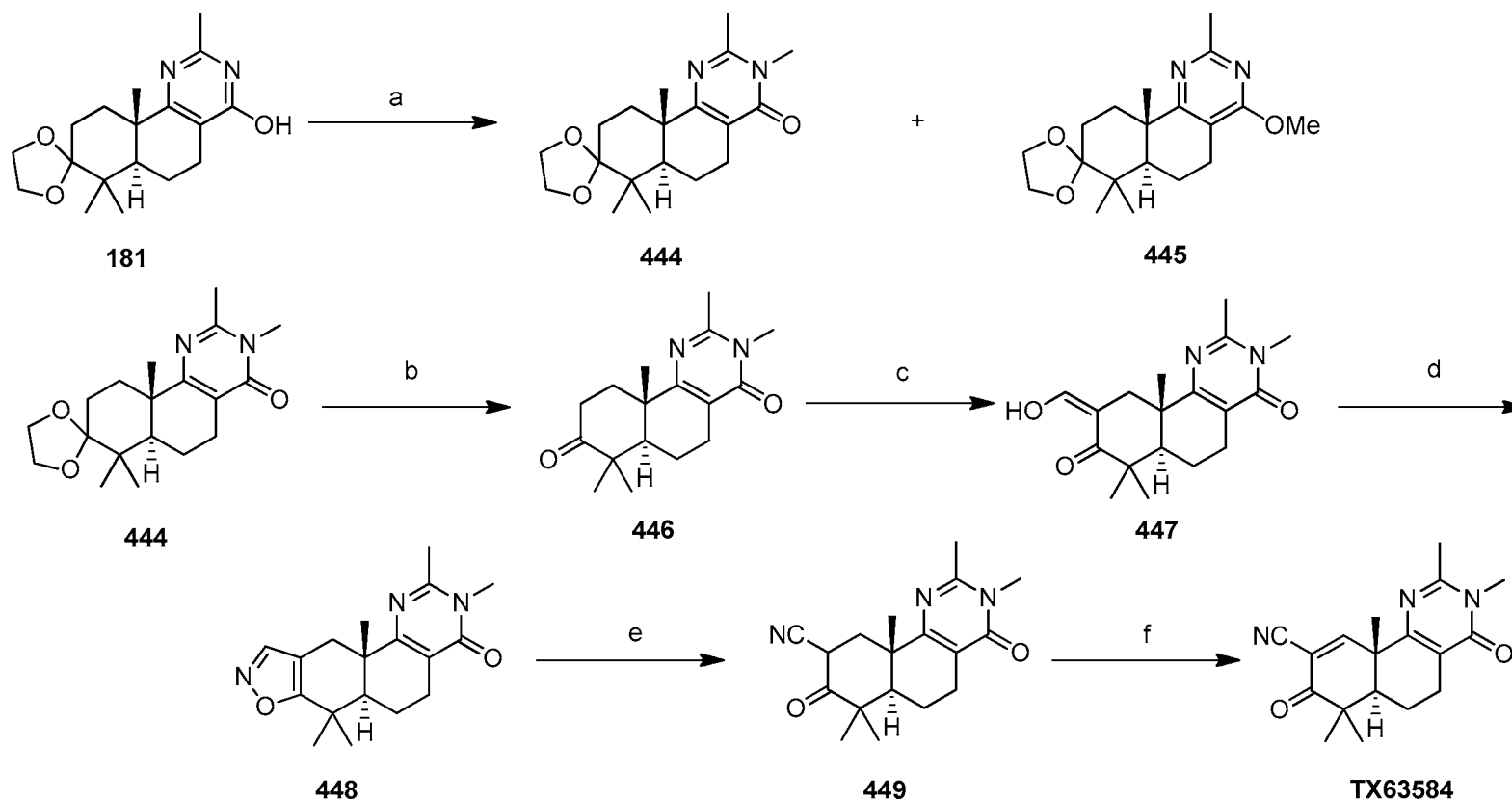
Reagents and conditions pertaining to Schemes 85: (a) $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, DIPEA, DCM, then 2-pyridine carboxylic acid, chloride hydrochloride, RT, 16 hr; (b) $\text{NHNH}_2 \cdot \text{H}_2\text{O}$, EtOH, RT, 16 hr then 70 °C, 1 hr; (c) HCl (aq), MeOH, RT, 16 hr, 94%; (d) HCO_2Et , NaOMe, MeOH, RT, 16 hr, 96%; (e) $\text{NH}_2\text{OH} \cdot \text{HCl}$, EtOH, H_2O , RT, 16 hr, 85%; (f) NaOMe, MeOH, THF, RT, 16 hr, 99%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 60 °C, 3 hr, 16%.

Scheme 86:



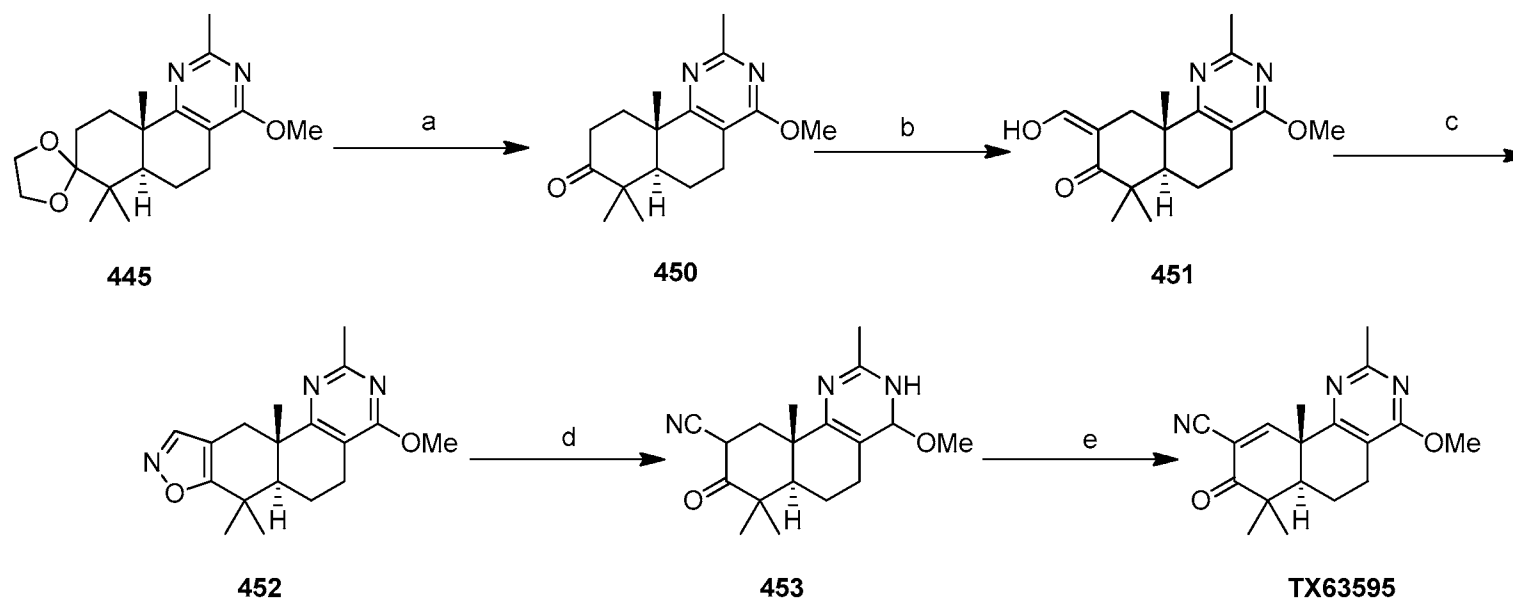
Reagents and conditions pertaining to Schemes 86: (a) Accufluor, MeCN, 80 °C, 2 hr then RT, 3 day, 14%.

Scheme 87:



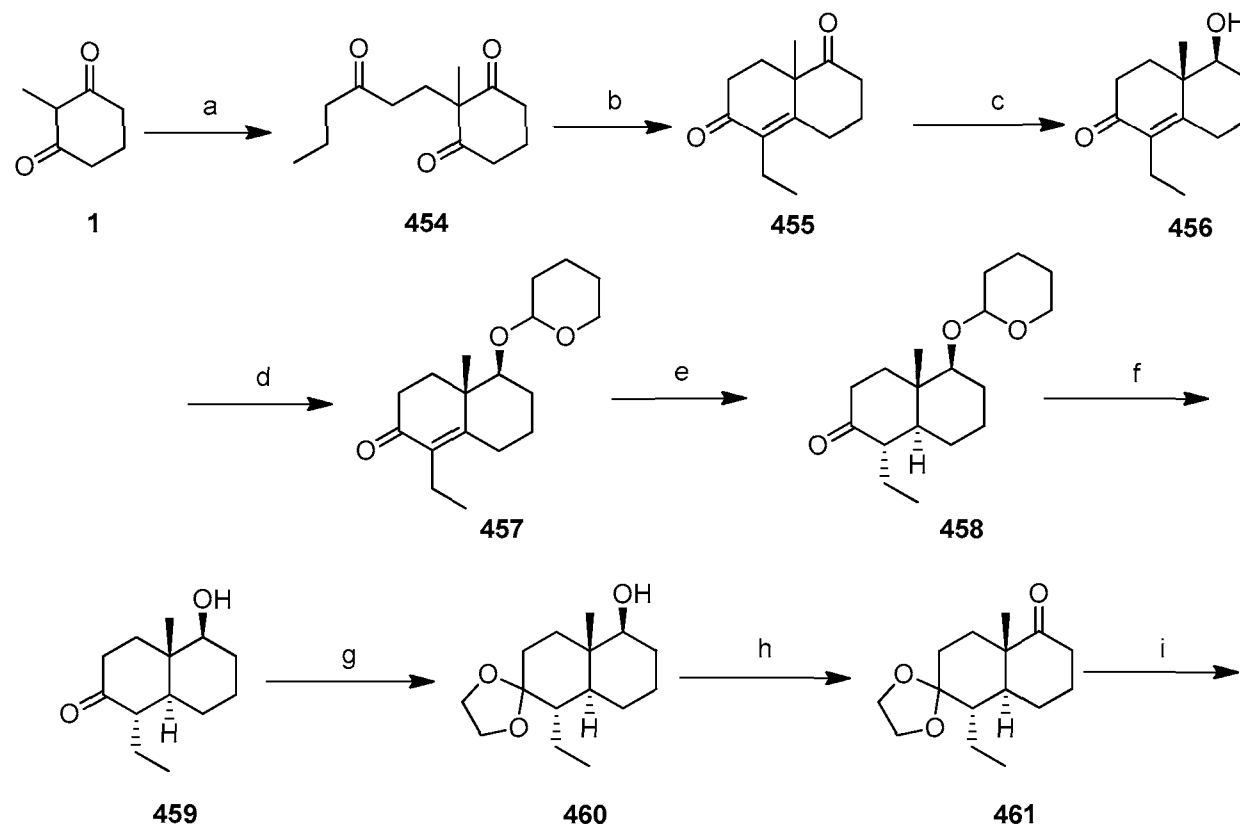
Reagents and conditions pertaining to Schemes 87: (a) MeOTf, TEA, DCM, RT, 16 hr, **444**: 33%, **445**: 10%; (b) HCl (aq), MeOH, RT, 16 hr, 93%; (c) HCO₂Et, NaOMe, MeOH, RT, 16 hr, 72%; (d) NH₂OH-HCl, EtOH, H₂O, 50 °C, 2hr then RT, 16 hr; (e) NaOMe, MeOH, RT, 16 hr; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 hr, 31%.

Scheme 88:

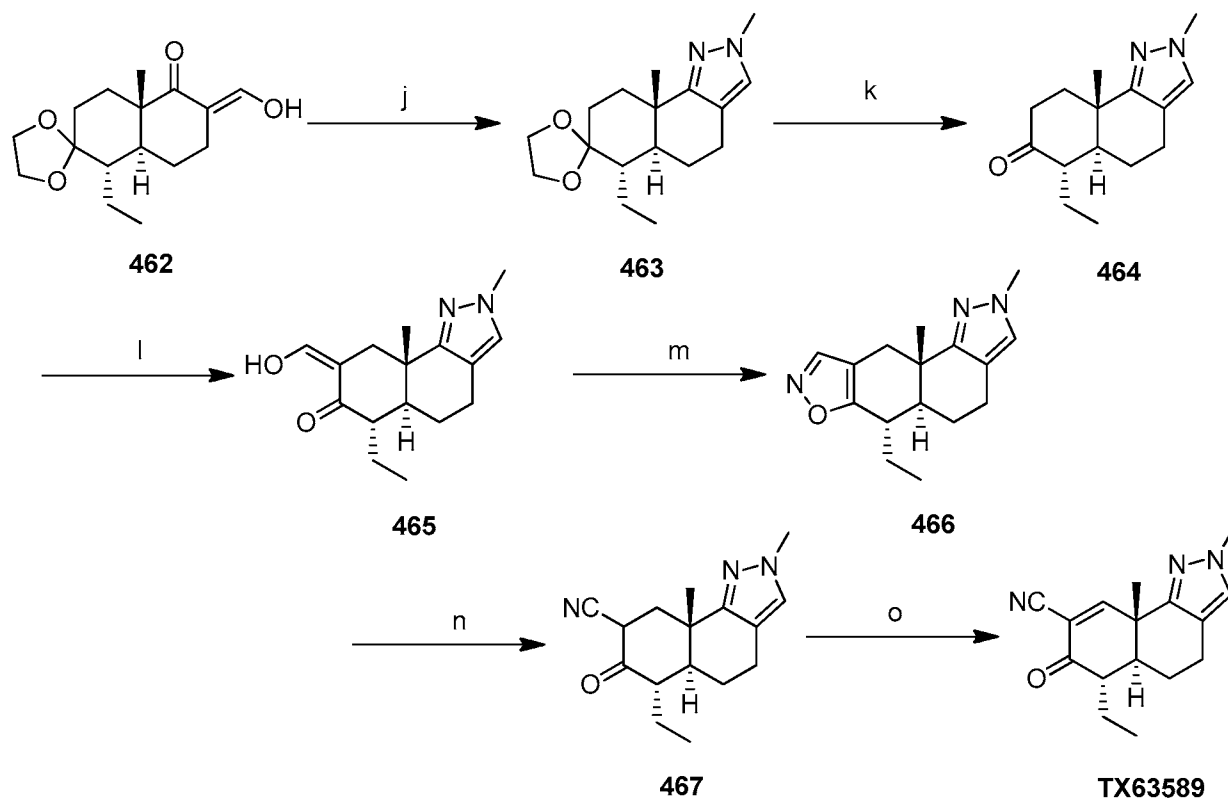


Reagents and conditions pertaining to Schemes 88: (a) HCl (aq), MeOH, THF, RT, 16 hr, 89%; (b) HCO₂Et, NaOMe, MeOH, RT, 16 hr; (c) NH₂OH-HCl, EtOH, H₂O, 50 °C, 16 hr, 85%; (d) NaOMe, MeOH, RT, 16 hr, 96%; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 hr, 39%.

Scheme 89 (a):



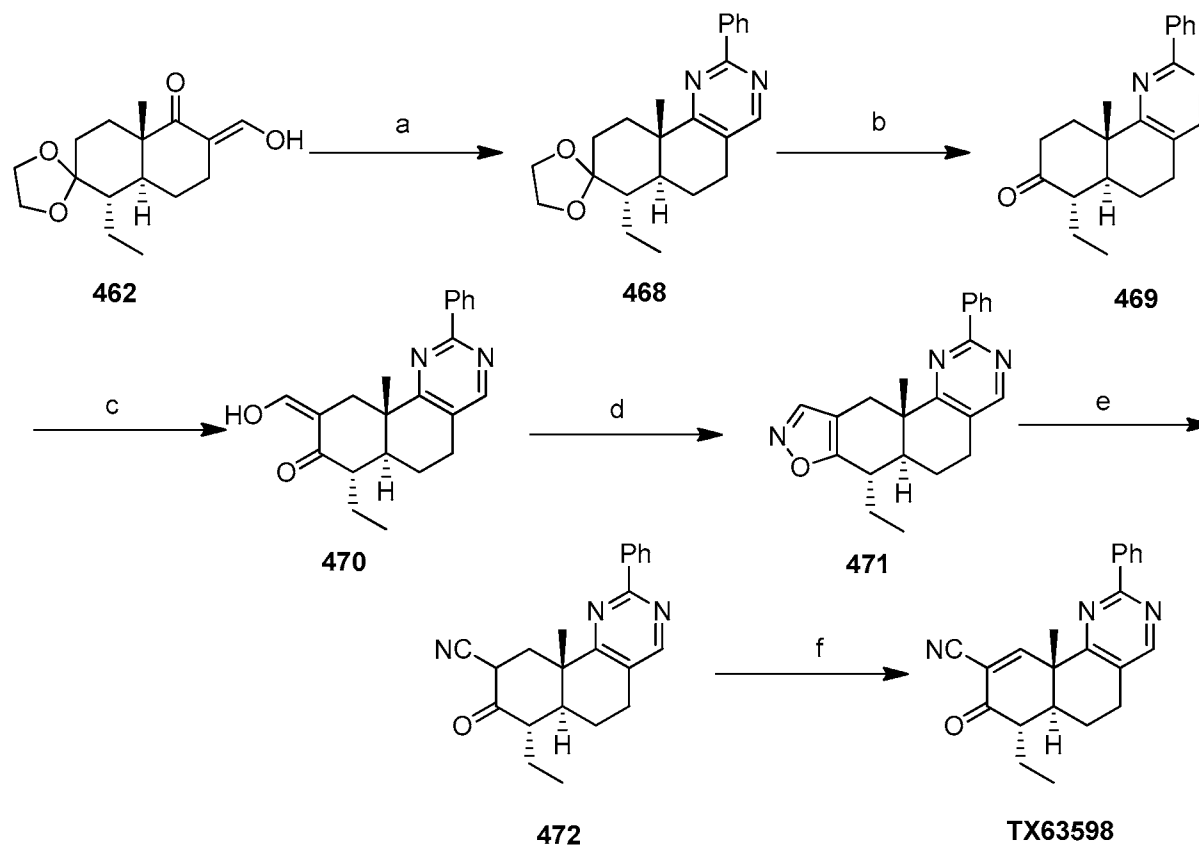
Scheme 89 (b):



Reagents and conditions pertaining to Schemes 89 (a) and (b): (a) 2-Methyl-1,3-cyclohexane-dione, 1-hexene-3-one, Et₃N, MeCN, RT 16 hr; (b) (S)-phenylalanine, CSA, MeCN, RT to 70 °C, 48 hr, 70%; (c) NaBH₄, EtOH, 0 °C, 15 min then AcOH, RT, 1 h, 96%; (d) 3,4-dihydro-2H-pyran, TsOH, CH₂Cl₂, 0 °C to RT, 16 hr, 46%; (e) Li, NH₃, -78 °C, 45 min, 68%; (f) pyridinium *p*-toluenesulfonate, EtOH, 70 °C, 6 hr then RT 16 hr; (g) Ethylene glycol, TsOH, benzene, reflux, 16 hr; (h) PDC, MgSO₄, DCM, RT 24 hr, 67%; (i) HCO₂Et, Benzene, then NaOMe, MeOH, 0 °C to rt, 16 hr, 97%; (j) MeNHNH₂, EtOH, 50 °C, 16 hr, 78%; (k) HCl (aq), MeOH, RT, 16 hr; (l) HCO₂Et, NaOMe, MeOH, RT, 16 hr, 98%; (m)

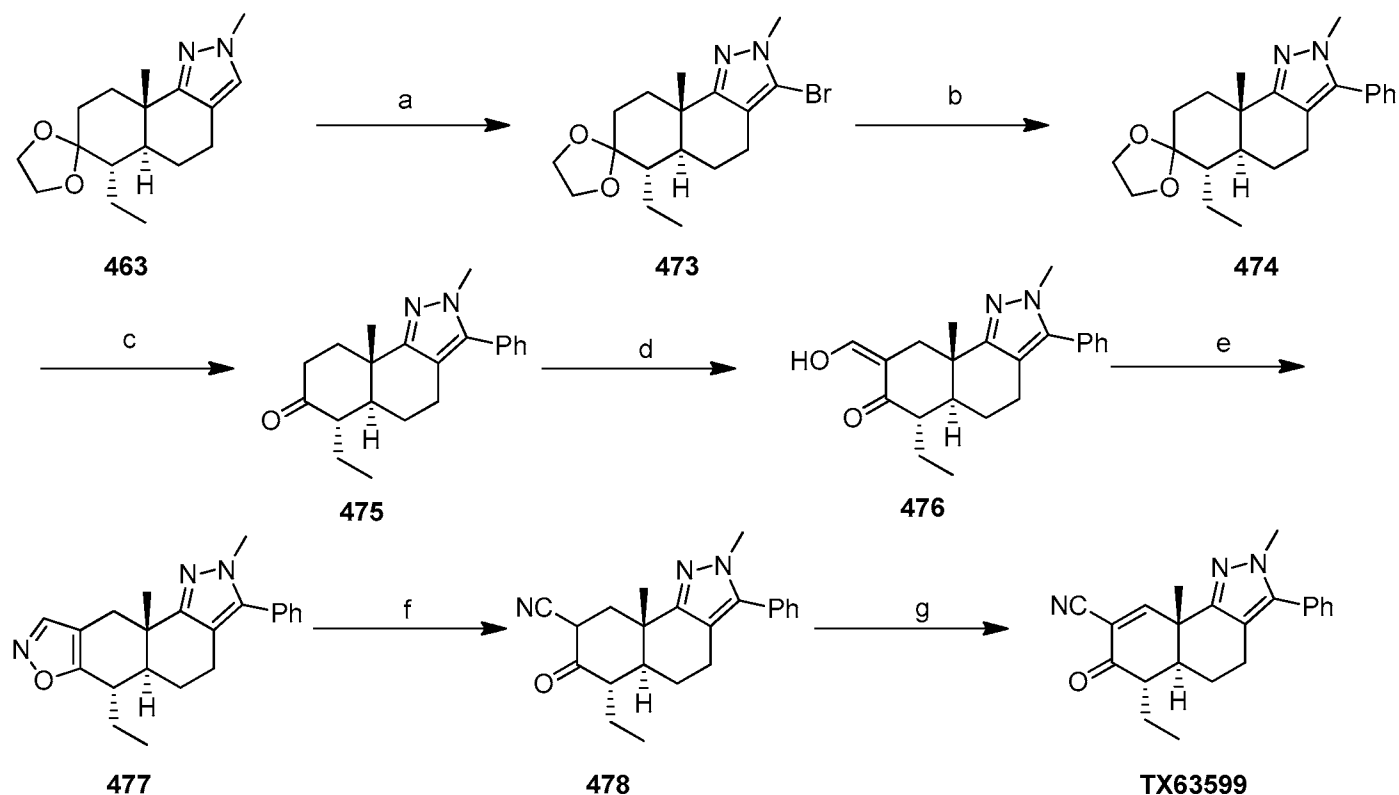
NH₂OH-HCl, EtOH, H₂O, 50 °C, 16 hr, 93%; (n) NaOMe, MeOH, RT, 16 hr, 83%; (o) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 hr, 30%.

Scheme 90:



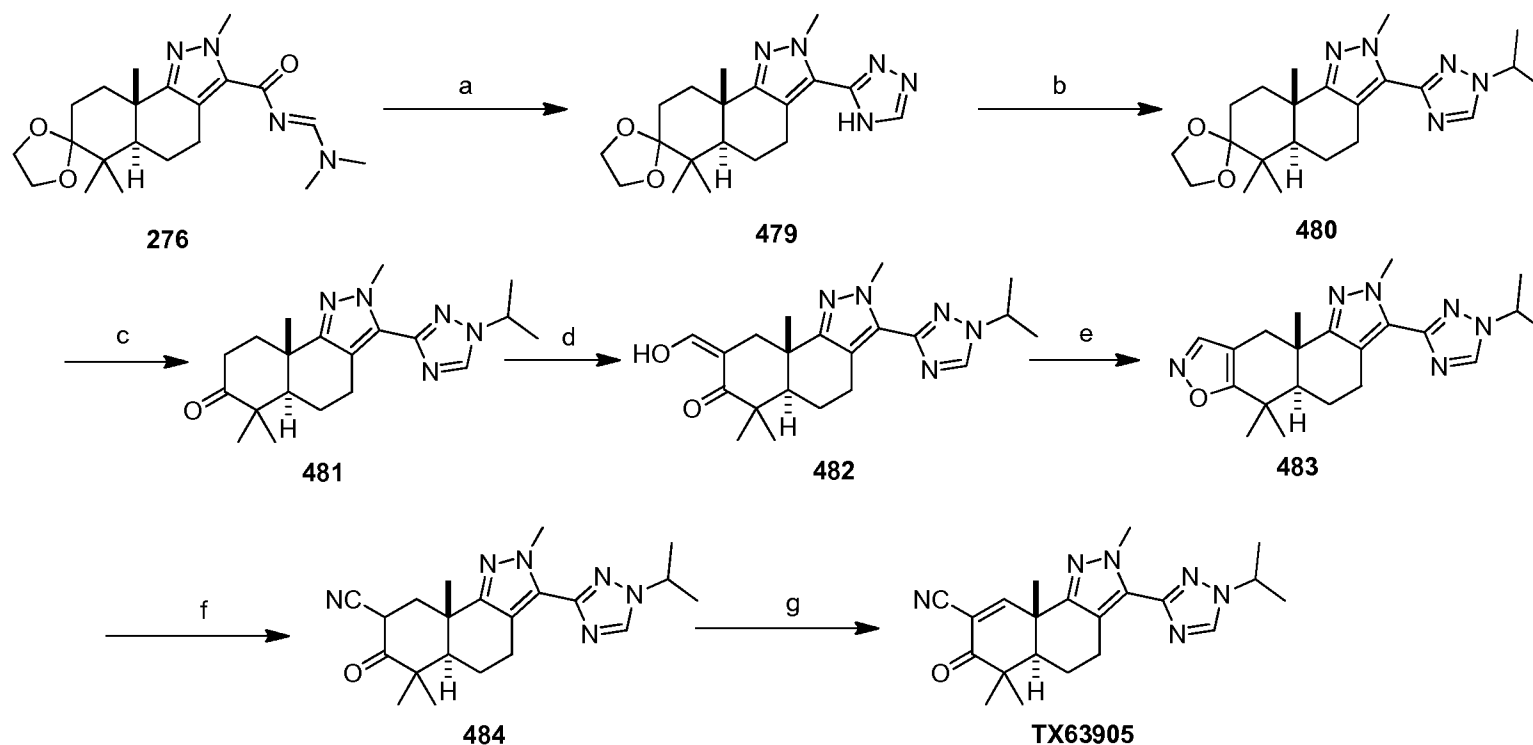
- 5 Reagents and conditions pertaining to Schemes 90: (a) Benzamidine hydroxchloride, piperidine, iPrOH, 85 °C, 96 hr; (b) HCl (aq), MeOH, THF, RT, 16 hr; (c) HCO₂Et, Benzene, then NaOMe, MeOH, RT, 16 hr; (d) NH₂OH-HCl, EtOH, H₂O, 50 °C, 16 hr; (e) NaOMe, MeOH, RT, 16 hr, 52%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 hr, 79%.

Scheme 91:

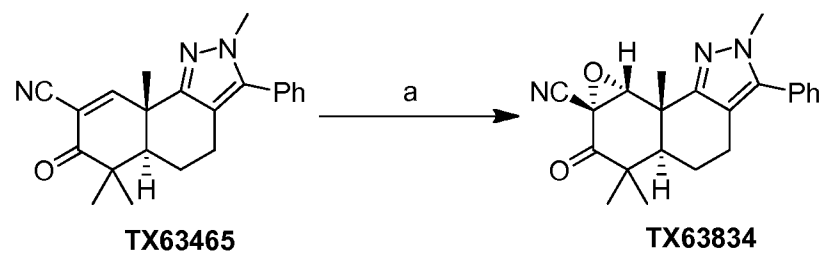


Reagents and conditions pertaining to Schemes 91: (a) 1,3-dibromo-5,5-dimethylhydantoin, DCM, RT, 30 min, 58%; (b) phenylboronic acid, Pd(PPh₃)₄, K₃PO₄, DME, 80 °C, 16 hr, 41%; (c) HCl (aq), MeOH, THF, RT, 16 hr, 92%; (d) HCO₂Et, Benzene, then NaOMe, MeOH, RT, 16 hr; (e) NH₂OH-HCl, EtOH, H₂O, 50 °C, 16 hr; (f) NaOMe, MeOH, RT, 16 hr; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1 h; (ii) pyridine, 50 °C, 16 hr, 30%.

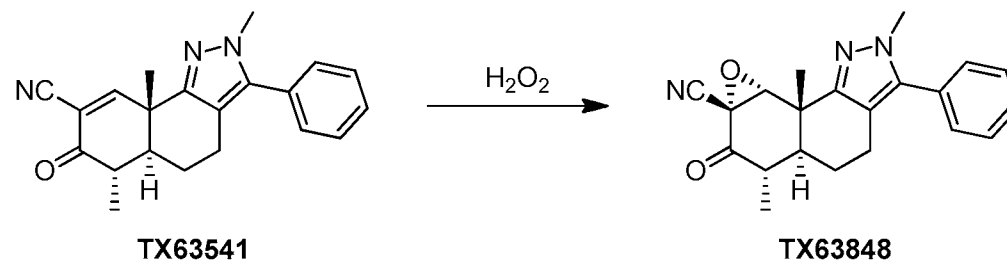
Scheme 92:



Reagents and conditions pertaining to Schemes 92: (a) $\text{N}_2\text{H}_4\text{-HCl}$, TEA, AcOH, dioxane, then **276**, 70 °C, 3 hr, 96%; (b) NaH, DMF, then iPrI, 16 hr, 79%; (c) HCl (aq), THF, RT, 48 hr, 97%; (d) HCO_2Et , THF then NaOMe, MeOH, RT, 16 hr, 98%; (e) $\text{NH}_2\text{OH-HCl}$, EtOH, H_2O , 50 °C, 3 hr, 100%; (f) NaOMe, MeOH, THF, 50 °C, 3 hr, 72%; (g) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1.5 h; (ii) pyridine, 60 °C, 4 hr, 69%.

Scheme 93:

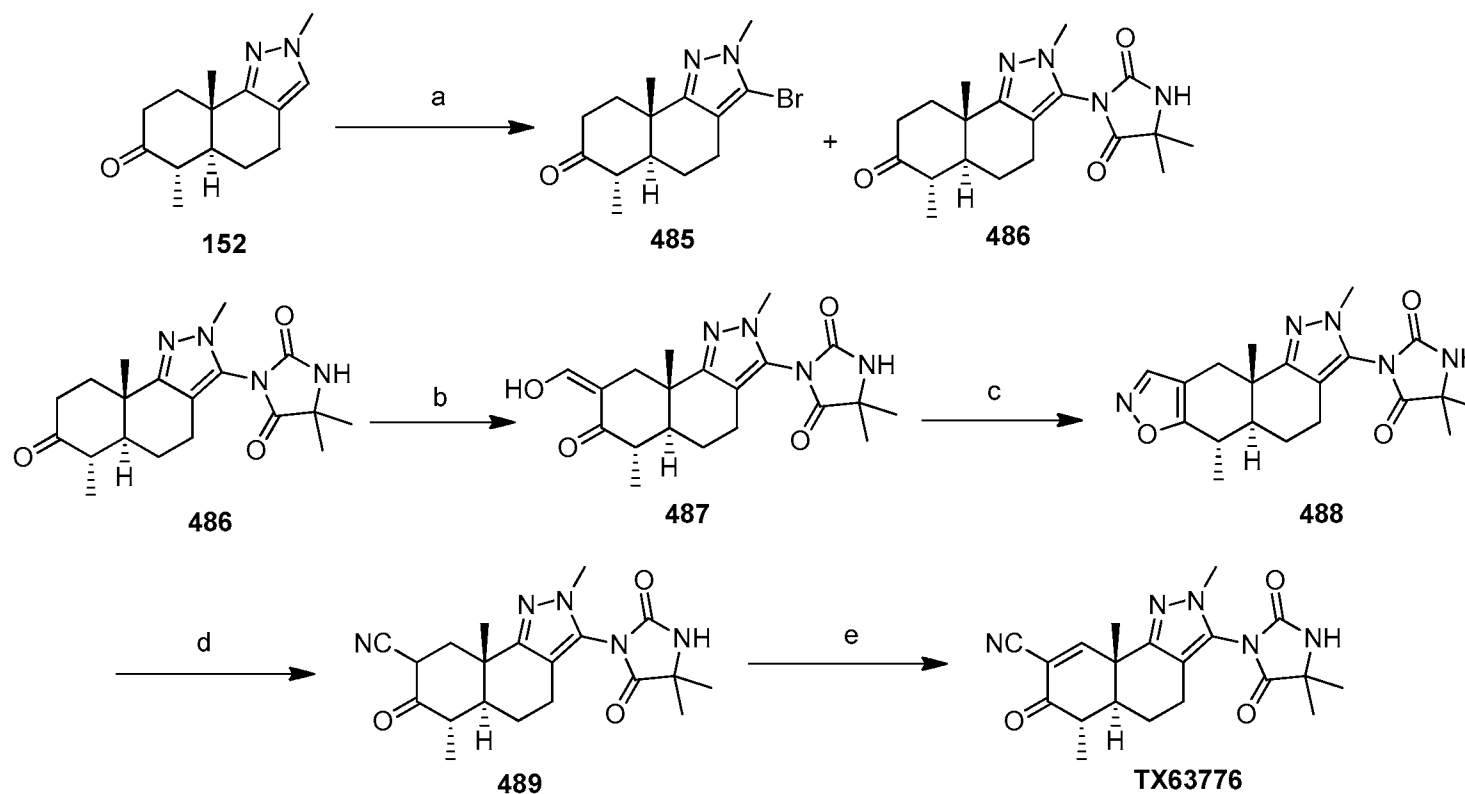
Reagents and conditions pertaining to Scheme 93: (a) H_2O_2 (aq), CH_3CN , RT, 16 hr, 85%.

Scheme 94:

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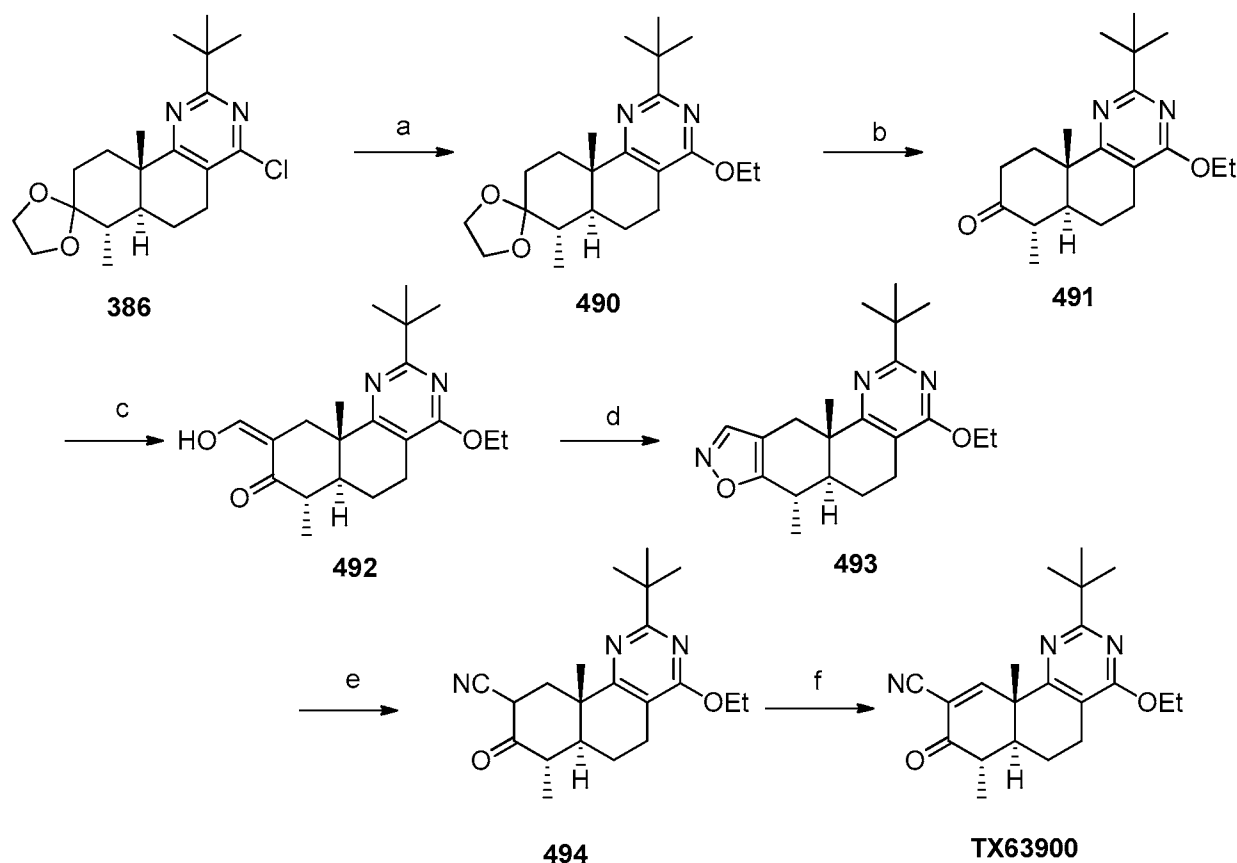
Reagents and conditions pertaining to Schemes 94: (a) H_2O_2 , MeCN , RT, 16 hr, 10%.

Scheme 95:



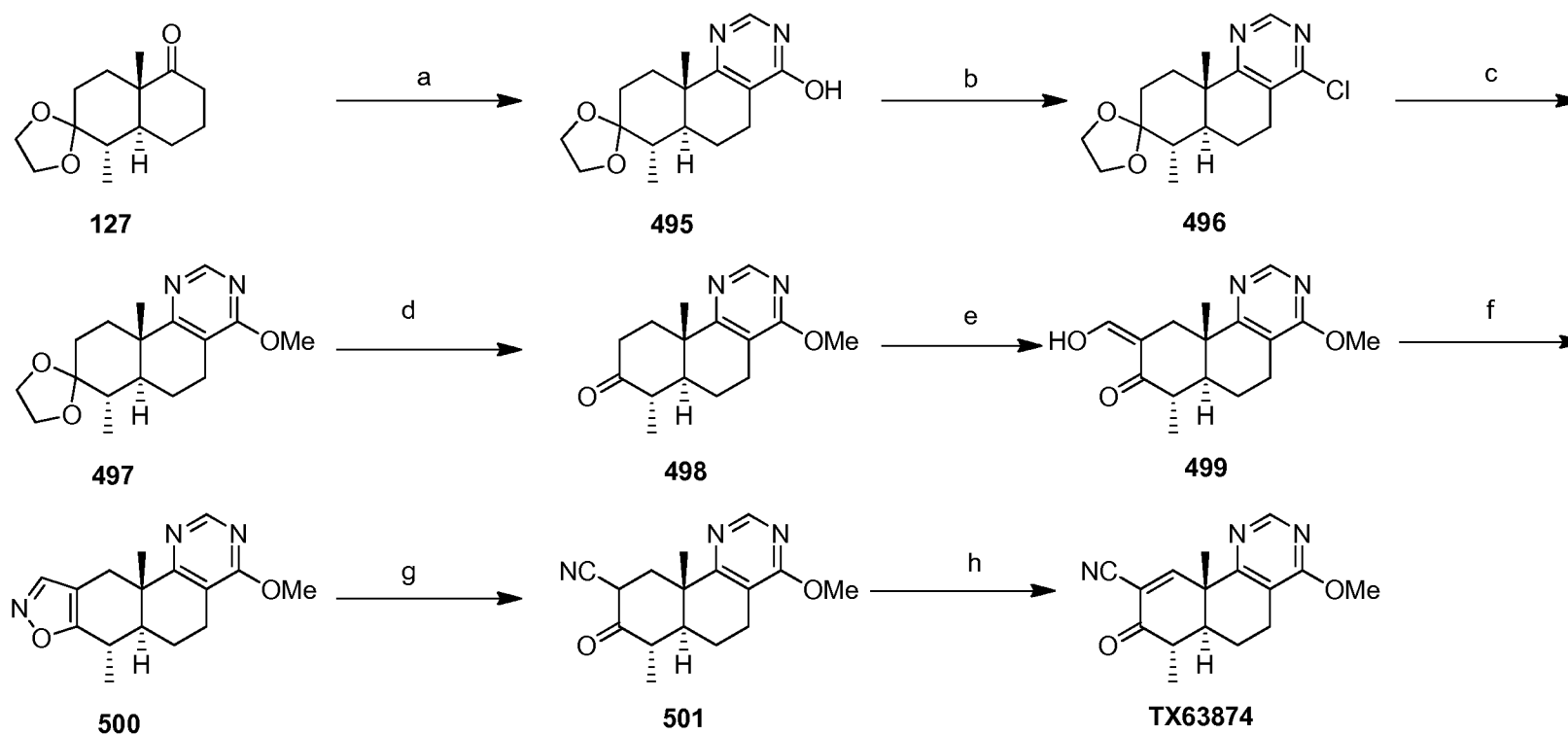
Reagents and conditions pertaining to Schemes 95: (a) 1,3-dibromo-5,5-dimethylhydantoin, DCM, 0 °C, 0.5 h, **485**: 55%, **486**: 14%; (b) HCO₂Et, benzene then NaOMe, MeOH, RT, 16 hr, 78%; (c) NH₂OH-HCl, EtOH, H₂O, 50 °C, 2 hr then RT 16 hr; (d) NaOMe, MeOH, THF, 5 RT, 16 hr, 81%; (e) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C, 1.0 h; (ii) pyridine, 50 °C, 2 hr, 27%.

Scheme 96:



Reagents and conditions pertaining to Schemes 96: (a) NaOEt, EtOH, 80 °C, 48 hr, 92%; (b) HCl (aq), EtOH, RT, 16 hr, 99%; (c) HCO₂Et, benzene, then NaOEt, EtOH, RT, 16 hr; (d) NH₂OH-HCl, EtOH, 50 °C, 2 hr, then RT, 16 hr, 88%; (e) NaOEt, EtOH, RT, 72 hr, 96%; (f) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 1 h; (ii) pyridine, 50 °C, 2 hr, 31%.

Scheme 97:



Reagents and conditions pertaining to Schemes 97: (a) (i) Dimethyl carbonate, NaH, THF, 80 °C, 16 hr; (ii) Formamidine acetate, piperidine, iPrOH, 80 °C, 48 hr, 16%; (b) POCl₃, DMF, DIPEA, 90 °C, 2 hr, 86%; (c) NaOMe, MeOH, 60 °C, 16 hr, 88%; (d) HCl, MeOH, RT, 16 hr, 99%; (e) HCO₂Et, NaOMe, benzene, MeOH, RT, 48 hr, 82%; (f) NH₂OH-HCl, EtOH, 50 °C, 16 hr, 95%; (g) NaOMe, MeOH, RT, 16 hr, 88%; (h) (i) 1,3-dibromo-5,5-dimethylhydantoin, DMF, 0 °C to RT, 2 h; (ii) pyridine, 50 °C, 2 hr, 30%.

Synthesis and Characterization of synthetic AIM Derivatives

Compound 2: Ethyl vinyl ketone (8.0 g, 95 mmol) was taken up in THF (75 mL) and compound **1** (10 g, 79 mmol) and triethylamine (8.37 g, 82 mmol) were added. The reaction was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated. The crude residue was purified by column chromatography (silica gel, 10 to 20 % EtOAc in Hexanes) to give compound **2** (13.5 g, 81%) as an oil. m/z 211 $[M+H]^+$.

Compound 3: Compound **2** (13.5 g, 64.2 mmol) was taken up in DMF (600 mL), the (*S*)-phenylalanine (10.63 g, 64 mmol) and D-camphorsulfonic acid (735 g, 32 mmol) were added. The reaction mixture was stirred at room temperature for 4 d, then heated to 70 °C for 1 d. The reaction mixture was cooled to room temperature, diluted with saturated NaHCO_3 (aq), and extracted with ether, then dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **3** (5.51 g, 45%) as an oil. m/z 193 $[M+H]^+$.

Compound 4: A solution of NaBH_4 (0.296 g, 7.8 mmol) in ethanol (40 mL) was added to a 0 °C solution of compound **3** (5.51 g, 28.6 mmol) in ethanol (100 mL). The reaction was stirred at 0 °C for 1 h and quenched with acetic acid (2.9 mL). The reaction mixture was warmed to room temperature and stirred for 5 min, then concentrated. The crude residue was purified by column chromatography (silica gel, 20 % EtOAc in Hexanes) to give compound **4** (5.0 g, 90%) as an oil. m/z 195 $[M+H]^+$.

Compound 5: Compound **4** (3.05 g, 15.6 mmol) was taken up in CH_2Cl_2 , then *i*- Pr_2EtN and MOMCl were added. The mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated. The residue was diluted with EtOAc, washed with 0.1 N HCl and brine, then dried with Na_2SO_4 , and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **5** (3.35 g, 90%) as a pale yellow liquid: m/z 239 $[M+H]^+$.

Compound 6: A solution of compound **5** (3.0 g, 12.6 mmol) and *t*-BuOH (965 mg, 13 mmol) in THF (10 mL) was added to a -78 °C solution of lithium wire (0.44 g, 64 mmol) in liq. NH_3 (50 mL). The mixture was stirred at reflux for 2 h and cooled to -78 °C. A solution of methyl iodide (9.5 g, 67 mmol) in THF (25 mL) was added. The reaction mixture was stirred at -78 °C for 2 h and quenched with water (2 mL),

then slowly warmed to room temperature. The mixture was extracted with ether, then washed with water and brine, dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 15 % EtOAc in Hexanes) to give compound **6** (0.90 g, 28%) as an oil. m/z 255 $[\text{M}+\text{H}]^+$.

5 **Compound 7:** A mixture of Compound **6** (0.90 g, 3.5 mmol), ethylene glycol, and camphorsulfonic acid in cyclohexane was heated to reflux for 16 h with azeotropic removal of water. The reaction mixture was cooled to room temperature, washed with saturated NaHCO_3 and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 20 % EtOAc in Hexanes) to give compound
10 **7** (0.59 g, 66%) as an oil. m/z 255 $[\text{M}+\text{H}]^+$.

Compound 8: Compound **7** (190 mg, 0.75 mmol) was taken up in CH_2Cl_2 and pyridinium dichromate and MgSO_4 were added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered through Celite, eluted with EtOAc/ CH_2Cl_2 (1/3), and concentrated to give compound **8** (180 mg,
15 95%) as a solid. m/z 253 $[\text{M}+\text{H}]^+$.

Compound 9: Compound **8** (120 mg, 0.48 mmol) was taken up in ethyl formate and cooled to 0 °C, then 30% sodium methoxide (30 wt% solution in MeOH) was added and the reaction warmed to room temperature. The reaction mixture was stirred at room temperature for 1 h, diluted with *t*-BuOMe and 1 N HCl, and extracted
20 with EtOAc, then washed with water, dried with MgSO_4 , and concentrated to give compound **9** (120 mg, 90%) as a solid. m/z 281 $[\text{M}+\text{H}]^+$.

Compounds 10 and 11: A mixture of **9** (120 mg, 0.43 mmol) and methyl hydrazine (35 mg, 0.7 mmol) in ethanol (15 mL) was heated to 60 °C for 2 h. The reaction mixture was concentrated. The crude residue was filtered through a short
25 plug of silica (eluted with EtOAc) and concentrated to give **10** and **11** (125 mg, quantitative) as an oil. m/z 291 $[\text{M}+\text{H}]^+$.

Compounds 12 and 13: The mixture of compounds **10** and **11** (0.40 g, 1.4 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with
30 saturated NaHCO_3 and extracted with ether, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 15 % EtOAc in Hexanes) to give compounds **12** and **13** (0.20 g, 59%) as a solid. m/z 247 $[\text{M}+\text{H}]^+$.

Compounds 14 and 15: A solution of compounds **12** and **13** (0.20 g, 0.81 mmol) in THF was added to a -78 °C solution of LDA (2.0 equiv.) in THF. The

reaction was stirred at -78 °C for 45 min, then a solution of TsCN (1.5 equiv.) in THF was added. The reaction was stirred at -78 °C for an additional 45 min, then quenched with 1 N HCl (aq) and warmed to room temperature. The reaction mixture was extracted with ether, then washed with water and brine, dried with MgSO₄, and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 25 % EtOAc in Hexanes) to give compounds **14** and **15** (170 mg, 77%) as a solid. m/z 272 [M+H]⁺.

Compounds TX63341 and TX63342: The mixture of compounds **14** and **15** (170 mg, 0.63 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 55 °C overnight. The reaction mixture was diluted with *t*-BuOMe and washed with water, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 25 % EtOAc in Hexanes) to give compound **TX63342** (39 mg, 23%) as a solid. ¹H NMR (400 MHz, *d*₆-DMSO) δ 8.44 (s, 1H), 7.39 (s, 1H), 3.78 (s, 3H), 2.69 (dd, 1H, *J* = 5.6, 15.7 Hz), 2.46 (ddd, 1H, *J* = 6.9, 11.6, 15.9 Hz), 2.16 (d, 1H, *J* = 11.6 Hz), 1.82 (m, 2H), 1.40 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H); m/z 270 [M+H]⁺, and **TX63341** (15 mg, 9%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ 8.30 (s, 1H), 7.31 (s, 1H), 4.06 (s, 3H), 2.75 (dd, 1H, *J* = 4.8, 15.7 Hz), 2.53 (ddd, 1H, *J* = 6.0, 12.3, 15.6 Hz), 2.27 (d, 1H, *J* = 11.9 Hz), 1.95 (dd, 1H, *J* = 5.6, 13.3 Hz), 1.77 (m, 1H), 1.53 (s, 3H), 1.31 (s, 6H); m/z 270 [M+H]⁺.

Compound 17: Compound **16** (10 g, 56 mmol) was taken up in ethanol, cooled to 0 °C, and a solution of NaBH₄ in ethanol added. The mixture was stirred at 0 °C for 2 h, and quenched with acetic acid. The reaction mixture was concentrated. The crude residue was filtered through a short plug of silica (eluted with 30 % EtOAc in Hexanes) and concentrated to give **17** (9.3 g, 92%) as a viscous liquid.

Compound 18: Compound **17** (9.3 g, 52 mmol) was taken up in CH₂Cl₂, then *i*-Pr₂EtN and MOMCl were added. The mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated. The residue was diluted with EtOAc, washed with 0.1 N HCl and brine, then dried with Na₂SO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 30 % EtOAc in Hexanes) to give compound **18** (9.0 g, 78%) as a pale yellow liquid: m/z 225 [M+H]⁺.

Compound 19: Compound **18** (3.5 g, 16 mmol) was taken up in *t*-BuOH, and a solution of KO*t*-Bu in THF was added. The mixture was stirred at room temperature for 10 min, cooled to 10 °C, and iodomethane was added. The reaction mixture was warmed to room temperature over 30 min and quenched with water. The mixture was extracted with EtOAc and washed with brine, then dried with Na₂SO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 10 % EtOAc in Hexanes) to give compound **19** (1.7 g, 43%) as a pale yellow liquid: *m/z* 253 [M+H]⁺.

Compound 20: A mixture of Compound **19** (4.31 g, 17.1 mmol), ethylene glycol, and *p*-toluenesulfonic acid hydrate in toluene was heated to reflux overnight with azeotropic removal of water. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with saturated NaHCO₃ and brine, then dried with MgSO₄ and concentrated to give **20** (4.26 g, 99%) as a solid. *m/z* 253 [M+H]⁺.

Compound 21: Compound **20** (4.65 g, 18.4 mmol) was taken up in EtOH under N₂ and 10% Pd/C added. The flask was rigorously purged with H₂ and stirred for 4 d at room temperature adding an additional portion of 10% Pd/C after 3 d. The reaction mixture was filtered through Celite, eluted with methanol, and concentrated to give compound **21** (4.63 g, 99%) as a solid. *m/z* 255 [M+H]⁺.

Compound 22: Compound **21** (58 mg, 0.28 mmol) was taken up in CH₂Cl₂, then *i*-Pr₂EtN and MOMCl were added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The reaction mixture was diluted with EtOAc, washed with saturated NaHCO₃ and brine, then dried with MgSO₄ and concentrated to give compound **22** (72 mg, quantitative) as a solid. *m/z* 255 [M+H]⁺.

Compound 23: A solution of **22** (70 mg, 0.28 mmol) in THF was added to a -78 °C solution of LDA (3.5 equiv.) in THF. The reaction was stirred at -78 °C for 30 min, then a solution of TsCN (1.3 equiv.) in THF was added. The reaction was stirred at -78 °C for an additional 30 min, then quenched with sat. NH₄Cl (aq) and warmed to room temperature. The reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 15 % EtOAc in Hexanes) to give compound **23** (51 mg, 66%) as a white solid. *m/z* 280 [M+H]⁺.

Compound TX63364: Compound **23** (48 mg, 0.17 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin (0.6 equiv.) was added, and the reaction stirred at 0 °C for 3 h adding an additional portion of 1,3-dibromo-5,5-dimethylhydantoin (0.1 equiv.) after 2 h. Then, pyridine
5 was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 60 °C for 4 h, then stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with 1N HCl (aq), saturated NaHCO₃ and brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 15 % EtOAc in Hexanes) to give compound
10 **TX63364** (41 mg, 86%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.94 (s, 1H), 4.78 (d, 1H, *J* = 6.8 Hz), 4.65 (d, 1H, *J* = 6.8 Hz), 3.44 (s, 3H), 3.28 (dd, 1H, *J* = 4.3, 11.4 Hz), 2.00 (m, 1H), 1.92 (m, 1H), 1.59 (m, 3H), 1.49 (m, 1H), 1.36 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H); *m/z* 278 [M+H]⁺.

Compound TX63363: Compound **TX63364** (28 mg, 0.10 mmol) was taken
15 up in THF, and 3 N HCl (aq) was added. The mixture was stirred 2 d at room temperature, and quenched with saturated NaHCO₃. The mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **TX63363** (16 mg, 68%) as a white solid. ¹H NMR (500 MHz,
20 CDCl₃) δ 8.06 (s, 1H), 8.52 (s, 1H), 3.45 (dd, 1H, *J* = 4.3, 11.6 Hz), 1.92 (m, 1H), 1.86 (m, 1H), 1.61 (m, 3H), 1.44 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); *m/z* 234 [M+H]⁺.

Compound 25: Compound **21** (2.56 g, 10.1 mmol) was taken up in CH₂Cl₂ and pyridinium dichromate was added over 10 min. The reaction mixture was stirred
25 overnight at room temperature, then heated to 45 °C until the starting material was consumed, as reported by thin layer chromatography. The reaction mixture was filtered through Celite, eluted with CH₂Cl₂, and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **25** (2.36 g, 93%) as a solid. *m/z* 253 [M+H]⁺.

30 **Compound 26:** Compound **25** (2.95 g, 11.7 mmol) was taken up in ethyl formate and cooled to 0 °C, then sodium methoxide (30 wt% solution in MeOH) was added and the reaction warmed to room temperature. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and the pH adjusted to 7 with acetic acid. The mixture was extracted with ethyl acetate and

washed with brine (aq), then dried with MgSO_4 and concentrated to give compound **26** (3.27 g, quantitative) as a solid. m/z 281 $[\text{M}+\text{H}]^+$.

Compound 27: A mixture of **26** (1.50 g, 5.35 mmol) and methyl hydrazine (0.37 g, 8.03 mmol) in ethanol (100 mL) was heated to 60 °C for 2 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, EtOAc) to give **27** (1.50 g, 97%) as an oil. m/z 291 $[\text{M}+\text{H}]^+$.

Compound 28: Compound **27** (1.50 g, 5.17 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with saturated NaHCO_3 and extracted with ether, then dried with MgSO_4 and concentrated to give compound **28** (1.10 g, 86%) as a solid. m/z 247 $[\text{M}+\text{H}]^+$.

Compound 29: A solution of **28** (1.10 g, 4.47 mmol) in THF was added to a -78 °C solution of LDA (1.6 equiv.) in THF. The reaction was stirred at -78 °C for 45 min, then a solution of TsCN (1.2 equiv.) in THF was added. The reaction was stirred at -78 °C for an additional 45 min, then quenched with 1 N HCl (aq) and warmed to room temperature. The reaction mixture was extracted with ether, dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 35 % EtOAc in Hexanes) to give compound **29** (0.53 g, 44%) as a solid. m/z 272 $[\text{M}+\text{H}]^+$.

Compounds TX63432 and TX63445: Compound **29** (530 mg, 1.95 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 1 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated, diluted with water, extracted with EtOAc, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 30 % EtOAc in Hexanes) to give compound **TX63432** (155 mg, 29%) as a solid. ^1H NMR (400 MHz, d_6 -DMSO) δ 8.44 (s, 1H), 7.39 (s, 1H), 3.78 (s, 3H), 2.69 (dd, 1H, $J = 5.6, 15.7$ Hz), 2.46 (ddd, 1H, $J = 6.9, 11.6, 15.9$ Hz), 2.16 (d, 1H, $J = 11.6$ Hz), 1.82 (m, 2H), 1.40 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H); m/z 270 $[\text{M}+\text{H}]^+$, and **TX63445** (28 mg, 4%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.43 (s, 1H), 3.85 (s, 3H), 2.65 (d, 1H, $J = 6.2, 16.1$ Hz), 2.44 (ddd,

1H, $J = 7.0, 11.8, 16.3$ Hz), 2.15 (dd, 1H, $J = 1.6, 12.1$ Hz), 1.98 (dd, 1H, $J = 7.1, 13.5$ Hz), 1.87 (dq, 1H, $J = 6.2, 12.0$ Hz), 1.49 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H); m/z 348, 350 (1:1) $[M+H]^+$.

Compound 30: A solution of cyclohexylhydrazine hydrochloride (0.245 g, 1.5 eq) and triethyl amine (165 mg, 1.5eq) in EtOH (5 mL) was stirred at room temperature for 15 min. A solution of compound **26** (0.3 g, 1.07 mmol) in EtOH (5 mL) was added slowly, and the mixture was stirred at room temperature for 30 min. The reaction mixture was then heated at 60 °C 16 h and then concentrated. The crude residue was purified by column chromatography (5% to 35% EtOAc in Hexanes) to give compound **30** (0.14 g, 36%) as a gummy solid; m/z 359 $[M+H]^+$.

Compound 31: A solution of compound **30** (0.14 g, 0.39 mmol) in MeOH was treated with 3 N HCl (aq) and stirred at room temperature for 3 h. The reaction mixture was quenched by ether and saturated NaHCO_3 (aq). The organic layer was separated and dried with MgSO_4 , then filtered through a short column (silica gel, 15% EtOAc in Hexanes) to give compound **31** (0.12 g, 98%) as a solid. m/z 315 $[M+H]^+$.

Compound 32: A solution of lithium diisopropylamide (LDA) was prepared by addition of *n*-BuLi (1.6 M in hexane) to diisopropylamine in THF at 0 °C, stirring for 30 min, and then cooling the reaction to -78 °C. A solution of compound **31** (0.12 g, 0.39 mmol) in THF was added dropwise to the LDA solution. The reaction was stirred at -78 °C for 45 min, and then a solution of *p*-toulenesulfonyl cyanide in THF was added. After stirring 45 min, 1 N HCl (aq) was added. The reaction mixture was extracted with ether, and the combined organics were washed with water and brine, dried over MgSO_4 , filtered, and evaporated. The crude residue was purified by column chromatography (silica gel, 5% to 25 % EtOAc in Hexanes) to give compound **32** (60 mg, 46%) as a solid; m/z 340 $[M+H]^+$.

Compound TX63444: 1,3-Dibromo-5,5-dimethylhydantoin was added to a solution of compound **32** (60 mg, 0.17 mmol) in DMF at 0 °C. After stirring for 2 h, pyridine was added, and the reaction mixture was heated to 55 °C for 16 h. After cooling to room temperature, MTBE was added, and the mixture was washed with water, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 5% to 25% EtOAc in Hexanes) to give **TX63444** (35 mg, 59%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1H), 7.13 (s, 1H), 4.04 (tt, 1H, $J = 3.6, 11.7$ Hz), 2.79 (dd, 1H, $J = 5.2, 16.2$ Hz), 2.56 (ddd, 1H, $J = 6.9, 11.8, 15.9$ Hz), 2.21 (dd, 1H, $J = 2.4, 11.5$ Hz), 2.15 (m, 2H), 1.88 (m, 4H), 1.76 (m,

1H), 1.66 (m, 2H), 1.50 (s, 3H), 1.44 (m, 2H), 1.29 (s, 3H), 1.28 (m, 1H), 1.24 (s, 3H); m/z 338 [M+H]⁺.

Compounds 33 and 34: *tert*-Butylhydrazine hydrochloride (0.125 g, 1.0 mmol) was taken up in ethanol (25 mL). Triethylamine (0.18 mL, 1.3 mmol) was added, and the mixture was stirred at room temperature for approximately 30 min. Compound **26** (0.203 g, 0.72 mmol) was added, and the reaction mixture was heated to reflux for 5 h and then stirred overnight at room temperature. The reaction mixture was concentrated. The residue was extracted with ethyl acetate (50 mL) and washed with water (20 mL) and brine (10 mL), then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give two products, compound **33** (81 mg, 35%, less polar) and compound **34** (91 mg, 36%, more polar) as solids. Compound **33**: m/z 333 [M+H]⁺. Compound **34**: m/z 347 [M+H]⁺.

Compound 35: Compound **33** (81 mg, 0.24 mmol) was taken up in methanol, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted with ethyl acetate (50 mL) and washed with saturated NaHCO₃ (aq), then dried with MgSO₄ and concentrated to give compound **35** (70 mg, quantitative) as a solid. m/z 289 [M+H]⁺.

Compound 36: Compound **35** (70 mg, 0.24 mmol) was taken up in ethyl formate, and sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with KH₂PO₄ (aq), then dried with MgSO₄ and concentrated to give compound **36** (69 mg, 90%) as a solid. m/z 317 [M+H]⁺.

Compound 37: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **36** (69 mg, 0.218 mmol). A 9/1 mixture of ethanol/water was added, and 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 dried with MgSO₄ and concentrated to give compound **37** (70 mg, quantitative) as a solid. m/z 314 [M+H]⁺.

Compound 38: Compound **37** (70 mg, 0.224 mmol) was dissolved in a 3/1 methanol/THF mixture, and sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄ (aq), and the reaction mixture was concentrated. The residue was extracted with ethyl

acetate and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **38** (41 mg, 59%) as a solid. m/z 314 $[\text{M}+\text{H}]^+$.

Compound TX63450: Compound **38** (41 mg, 0.13 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. Dibromodimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **TX63450** (23 mg, 56%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.58 (s, 1H), 7.21 (s, 1H), 2.79 (dd, 1H, $J = 5.7, 15.7$ Hz), 2.56 (ddd, 1H, $J = 7.3, 11.5, 15.8$ Hz), 2.21 (dd, 1H, $J = 2.6, 11.4$ Hz), 1.87 (m, 2H), 1.56 (s, 9H), 1.49 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H); m/z 312 $[\text{M}+\text{H}]^+$.

Compound 39: Compound **34** (91 mg, 0.26 mmol) was taken up in methanol, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. Reaction mixture was extracted with ethyl acetate (50 mL) and washed saturated NaHCO_3 , then dried with MgSO_4 and concentrated to give compound **39** (68 mg, 86%) as a solid. m/z 303 $[\text{M}+\text{H}]^+$.

Compound 40: Compound **39** (68 mg, 0.22 mmol) was taken up in ethyl formate, and sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with KH_2PO_4 (aq), then dried with MgSO_4 and concentrated to give compound **40** (62 mg, 83%) as a solid. m/z 331 $[\text{M}+\text{H}]^+$.

Compound 41: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **40** (62 mg, 0.19 mmol). A 9/1 mixture of ethanol/water was added, and 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 dried with MgSO_4 and concentrated to give compound **41** (66 mg, quantitative) as a solid. m/z 328 $[\text{M}+\text{H}]^+$.

Compound 42: Compound **41** was dissolved in a 3/1 methanol/THF mixture, and sodium methoxide (30 wt% solution in MeOH) was added, and the reaction

mixture was stirred at 55 °C for 5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 , and the reaction mixture was concentrated. The residue was extracted with ethyl acetate and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by
5 column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **42** (49 mg, 80%) as a solid. m/z 328 $[\text{M}+\text{H}]^+$.

Compound TX63451: Compound **42** was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30
10 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel,
15 25 % EtOAc in Hexanes) to give compound **TX63451** (33 mg, 68%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.39 (s, 1H), 7.89 (s, 1H), 3.28 (dd, 1H, $J = 3.8, 16.6$ Hz), 3.06 (dd, 1H, $J = 12.2, 16.5$ Hz), 2.58 (dd, 1H, $J = 3.7, 12.1$ Hz), 1.71 (s, 9H), 1.44 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H); m/z 326 $[\text{M}+\text{H}]^+$.

Compound 43: A mixture of **26** (300 mg, 1.07 mmol) and (2,2,2-trifluoroethyl)hydrazine (70% pure, 270 mg, 2.4 mmol) in ethanol (25 mL) was
20 heated to 60 °C for 2 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 45 % EtOAc in Hexanes) to give **43** (270 mg, 70%) as a solid. m/z 359 $[\text{M}+\text{H}]^+$.

Compound 44: Compound **43** (0.27 g, 0.75 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. Reaction mixture was extracted with ethyl acetate (2×25 mL) and washed saturated NaHCO_3 , then dried with MgSO_4 and concentrated to give compound **44** (0.24 g, quantitative) as a solid. m/z 315 $[\text{M}+\text{H}]^+$.

Compound 45: Compound **44** (0.24 g, 0.75 mmol) was taken up in ethyl formate, and sodium methoxide (30 wt% solution in MeOH) was added. The mixture
30 was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with KH_2PO_4 (aq), then dried with MgSO_4 and concentrated to give compound **45** (0.25 g, 96%) as a solid. m/z 343 $[\text{M}+\text{H}]^+$.

Compound 46: A mixture of hydroxylamine hydrochloride and **45** (0.25 g, 0.73 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with ethyl acetate, then dried with MgSO₄ and concentrated to give compound **46** (0.23 g, 93%) as a solid. m/z 340 [M+H]⁺.

Compound 47: Compound **46** (0.23 g, 0.68 mmol) was dissolved in a 1/1 methanol/THF mixture, and sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH₂PO₄. The mixture was extracted with ethyl acetate and washed with brine, then dried with MgSO₄ and concentrated to give compound **47** (0.12 g, 52%) as a solid. m/z 340 [M+H]⁺.

Compound TX63454: Compound **47** (0.12 g, 0.35 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 30 % EtOAc in Hexanes) to give compound **TX63454** (65 mg, 54%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H), 7.22 (s, 1H), 4.65 (m, 2H), 2.84 (dd, 1H, *J* = 5.7, 16.2 Hz), 2.59 (ddd, 1H, *J* = 7.0, 11.9, 16.1 Hz), 2.21 (dd, 1H, *J* = 2.1, 11.9 Hz), 1.90 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); m/z 338 [M+H]⁺.

Compounds 48 and 49: Ethanol was added to a mixture of **26** (204 mg, 0.73 mmol), phenylhydrazine hydrochloride (132 mg, 0.92 mmol), and sodium acetate trihydrate (140 mg, 1.08 mmol) was gradually heated to 65 °C. The reaction mixture was then stirred at 70 °C overnight. The reaction mixture was concentrated. The reaction mixture was extracted with ethyl acetate and washed with saturated NaHCO₃, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give **48** (91 mg, 35%, less polar) and **49** (135 mg, 51%, more polar) as solids. Compound **48**: ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, 2H, *J* = 8.5 Hz), 7.53 (s, 1H), 7.41 (t, 2H, *J* = 7.6 Hz), 7.22 (t, 1H, *J* = 7.5 Hz), 3.98 (m, 4H), 2.80 (dd, 1H, *J* = 5.7, 15.9 Hz), 2.59 (ddd, 1H, *J* = 6.5, 11.6, 15.8 Hz), 2.36 (m, 1H), 1.99 (m, 2H), 1.77 (m, 4H), 1.37 (s, 3H), 1.09 (3H), 0.98 (s, 3H); m/z 353 [M+H]⁺. Compound **49**: ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s,

1H), 7.56 (m, 4H), 7.46 (m, 1H), 3.93 (m, 4H), 2.98 (dd, 1H, $J = 12.2, 16.7$ Hz), 2.86 (dd, 1H, $J = 4.0, 16.7$ Hz), 2.32 (dd, 1H, $J = 4.0, 12.2$ Hz), 2.01 (m, 1H), 1.91 (m, 2H), 1.68 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 0.90 (s, 3H); m/z 367 $[M+H]^+$.

Compound 50: Compound **48** (86 mg, 0.24 mmol) was taken up in methanol, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. Reaction mixture was extracted with ethyl acetate (50 mL) and washed saturated NaHCO_3 , then dried with MgSO_4 and concentrated to give compound **50** (69 mg, 92%) as a solid. m/z 309 $[M+H]^+$.

Compound 51: Compound **50** (69 mg, 0.22 mmol) was taken up in ethyl formate, and sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with KH_2PO_4 (aq), then dried with MgSO_4 and concentrated to give compound **51** (73 mg, 97%) as a solid. m/z 337 $[M+H]^+$.

Compound 52: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **51** (73 mg, 0.22 mmol). A 9/1 mixture of ethanol/water was added, and 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 dried with MgSO_4 and concentrated to give compound **52** (66 mg, 91%) as a solid. m/z 334 $[M+H]^+$.

Compound 53: Compound **52** (66 mg, 0.20 mmol) was dissolved in a 3/1 methanol/THF mixture, and sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 , and the reaction mixture was concentrated. The residue was extracted with ethyl acetate and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **53** (53 mg, 80%) as a solid. m/z 334 $[M+H]^+$.

Compound TX63455: Compound **53** (53 mg, 0.16 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and washed with brine, then dried

with MgSO_4 and concentrated. The crude residue was purified by repeated column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **TX63455** (1.8 mg, 3%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.63 (s, 1H), 7.66 (m, 3H), 7.48 (m, 3H), 2.92 (dd, 1H, $J = 4.8, 15.8$ Hz), 2.67 (ddd, 1H, $J = 6.5, 11.8, 15.8$ Hz),
5 2.26 (dd, 1H, $J = 2.4, 11.4$ Hz), 1.97 (m, 2H), 1.58 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H);
 m/z 332 $[\text{M}+\text{H}]^+$.

Compound 54: Compound **49** (0.120 g, 0.33 mmol) was taken up in methanol (20 mL), and 1N HCl (aq, 2 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated. The residue was taken up
10 in ethyl acetate (50 mL) and washed with saturated NaHCO_3 (aq, 15 mL), then dried with MgSO_4 and concentrated to give compound **54** (97.3 mg, 92%) as a solid.

Compound 55: Compound **54** (0.0973 g, 0.30 mmol) was taken up in ethyl formate (5 mL), and sodium methoxide (30 wt% solution in MeOH, 0.4 mL, 7.1 mmol) was added. The mixture was stirred overnight at room temperature. The
15 reaction mixture was extracted with ethyl acetate and washed with KH_2PO_4 (aq), then dried with MgSO_4 and concentrated to give compound **55** (100.7 mg, 95%) as a solid.
 m/z 351 $[\text{M}+\text{H}]^+$.

Compound 56: A solution of 0.1 N hydroxylamine hydrochloride (aq, 3.2 mL, 0.32 mL) was added to compound **55** (100.7 mg, 0.29 mmol). A 9/1 mixture of
20 ethanol/water (2 mL) was added, and 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 dried with MgSO_4 and concentrated to give compound **56** (75.4 mg, 76%) as a solid. m/z 348 $[\text{M}+\text{H}]^+$.

Compound 57: Compound **56** (75.4 mg, 0.22 mmol) was dissolved in a 3/1
25 methanol/THF mixture (6 mL), and sodium methoxide (30 wt% solution in MeOH, 0.24 mL, 4.3 mL) was added, and the reaction mixture was stirred at 55 °C for approximately 5.5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 , and the reaction mixture was concentrated. The residue was extracted with ethyl acetate (50 mL) and washed with
30 brine (10 mL), then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **57** (59.5 mg, 79%) as a solid. m/z 348 $[\text{M}+\text{H}]^+$.

Compound TX63456: Compound **57** (59.5 mg, 0.17 mmol) was dissolved in dry DMF (1 mL), and the solution was cooled to 0 °C. Dibromodimethylhydantoin

(31 mg, 0.109 mmol) was added, and the reaction stirred at 0 °C until the starting material was consumed, as reported by thin layer chromatography. Then, pyridine (0.13 mL, 1.6 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (60 mL) and washed with brine (10 mL), then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give a solid (29.9 mg). The purified residue was purified again by column chromatography (silica gel, 25 % EtOAc in Hexanes) to a solid. The solid was triturated with Et₂O/EtOAc to give compound **TX63456** (14.3 mg, 24%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (s, 1H), 8.15 (s, 1H), 7.48-7.68 (m, 5H), 3.18 (dd, 1H, *J* = 8.0, 16.0 Hz), 3.02 (dd, 1H, *J* = 4.0, 16.0 Hz), 2.62 (dd, 1H, *J* = 4.0, 12.0 Hz), 1.56 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); *m/z* 346 [M+H]⁺.

Compound 58: Compound **26** (1.200 g, 4.28 mmol) was taken up in ethanol (100 mL). Anhydrous hydrazine (0.36 mL, 11.5 mmol) in ethanol (5 mL) was added, and the mixture was stirred at room temperature for 2 h and then 60 °C for 1 h. The reaction mixture was concentrated. The residue was triturated with ether/ethyl acetate to give compound **58** (0.965 g, 82%) as a solid. *m/z* 277 [M+H]⁺.

Compound 59: Compound **58** (280 mg, 1.01 mmol) was taken up in methanol, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted with ethyl acetate and washed with saturated NaHCO₃ (aq), then dried with MgSO₄ and concentrated to give compound **59** (245.2 mg, quantitative) as a solid. *m/z* 233 [M+H]⁺.

Compound 60: Compound **59** (239 mg, 1.03 mmol) was taken up in ethyl formate, and sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with KH₂PO₄ (aq), then dried with MgSO₄ and concentrated to give compound **63** (264 mg, 99%); *m/z* 261 [M+H]⁺.

Compound 61: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **60** (260 mg, 1.00 mmol). A 9/1 mixture of ethanol/water was added, and 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 dried with MgSO_4 and concentrated to give compound **61** (248.9 mg, 97%): m/z 258 $[\text{M}+\text{H}]^+$.

Compound 62: Compound **61** (245 mg, 0.95 mmol) was dissolved in a 3/1 methanol/THF mixture, and sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 , and the reaction mixture was concentrated. The residue was extracted with ethyl acetate and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **62** (204 mg, 83%) as a solid. m/z 258 $[\text{M}+\text{H}]^+$.

Compound TX63467: A mixture of compound **62** (51 mg, 0.198 mmol) and DDQ (59 mg, 0.26 mmol) were taken up in benzene (11 mL). The mixture was stirred at reflux for 4.5 h. After cooling to room temperature, the reaction mixture was concentrated. The crude residue was purified by column chromatography three times (silica gel, 1.5% MeOH in CH_2Cl_2 , 2% MeOH in CH_2Cl_2 and EtOAc, respectively) to give a solid. The purified residue was taken up in ethyl acetate (40 mL) and washed with saturated NaHCO_3 (aq), then dried with MgSO_4 and concentrated to give compound **TX63467** (22 mg, 43%) as a solid. ^1H NMR (400 MHz, CD_3OD) δ 12.59 (s, 1H), 8.51 (s, 1H), 7.44 (s, 1H), 2.68-2.77 (m, 1H), 2.45-2.58 (m, 1H), 2.15-2.22 (m, 1H), 1.78-1.92 (m, 2H), 1.41 (s, 3H), 1.21 (s, 3H), 1.13 (s, 3H); m/z 256 $[\text{M}+\text{H}]^+$.

Compound TX63462: **TX63467** (12 mg, 0.047 mmol) was taken up in a mixture of saturated NaHCO_3 (aq, 0.5 mL) and THF (1.5 mL), and the mixture was cooled to 0 °C. Methyl chloroformate (1 drop, excess) was added and the reaction mixture was stirred 40 min at 0 °C and then more methyl chloroformate (2 drops, excess) was added and the reaction mixture was stirred 20 minutes. The reaction mixture was extracted with ethyl acetate (40 mL) and washed with NaCl (aq, 10 mL), then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **TX63462** (2.3 mg, 16%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.57 (s, 1H), 7.89 (s, 1H), 4.10 (s, 3H), 2.90 (dd, 1H, $J = 8.0, 16.0$ Hz), 2.58-2.68 (m, 1H), 2.19 (dd, 1H, $J = 4.0, 12.0$ Hz), 1.85-2.02 (m, 2H), 1.56 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H); m/z 314 $[\text{M}+\text{H}]^+$.

Compound TX63463: **TX63467** (12 mg, 0.047 mmol) was taken up in a mixture of saturated NaHCO_3 (aq, 0.5 mL) and THF (1.5 mL), and the mixture was cooled to 0 °C. Acetyl chloride (1 drop, excess) was added, and the reaction mixture

was stirred 40 min at 0 °C. Then more acetyl chloride (2 drops, excess) was added, and the reaction mixture was stirred an additional 20 minutes. The reaction mixture was extracted with ethyl acetate (40 mL) and washed with NaCl (aq, 10 mL), then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **TX63463** (3.3 mg, 24%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 7.97 (s, 1H), 2.90 (dd, 1H, *J* = 4.0, 12.0 Hz), 2.69 (s, 3H), 2.57-2.68 (m, 1H), 2.19 (dd, 1H, *J* = 4.0, 12.0 Hz), 1.85-2.02 (m, 2H), 1.54 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H); *m/z* 298 [M+H]⁺.

Compound 63: A mixture of **26** (300 mg, 1.07 mmol) and 2-hydrazinyethanol (130 mg, 1.7 mmol) in ethanol (5 mL) was heated to 60 °C for 2 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 1 % MeOH in EtOAc) to give **63** (320 mg, 93%) as an oil. *m/z* 321 [M+H]⁺.

Compound 64: Compound **63** (0.32 g, 1.0 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. Reaction mixture was extracted with ethyl acetate (2 × 25 mL) and washed saturated NaHCO₃, then dried with MgSO₄ and concentrated to give compound **64** (0.17 g, 62%) as a solid. *m/z* 277 [M+H]⁺.

Compound 65: Compound **64** (0.17 g, 0.62 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH₂PO₄ (aq), extracted with ethyl acetate (2 × 25 mL) and washed with brine, then dried with MgSO₄ and concentrated to give compound **65** (0.17 g, 91%) as a solid. *m/z* 305 [M+H]⁺.

Compound 66: A mixture of hydroxylamine hydrochloride and **65** (0.17 g, 0.56 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water, extracted with ethyl acetate (2 × 25 mL) and washed with brine, dried with MgSO₄ and concentrated to give compound **66** (0.18 g, quantitative) as a solid. *m/z* 302 [M+H]⁺.

Compound 67: Compound **66** (0.18 g, 0.56 mmol) was dissolved in a 1/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH₂PO₄. The mixture was

extracted with ethyl acetate (2 × 25 mL) and washed with brine, then dried with MgSO₄ and concentrated to give compound **67** (0.18 g, quantitative) as a solid. m/z 302 [M+H]⁺.

Compound TX63464: Compound **67** (0.18 g, 0.56 mmol) was dissolved in dioxane. Pyridinium bromide perbromide was added, and the reaction stirred at room temperature for 2 h. Pyridine was added, and the reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 2 % MeOH in EtOAc) to give compound **TX63464** (10 mg, 5%) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.17 (s, 1H), 4.21 (m, 2H), 4.01 (d, 1H, *J* = 5.1 Hz), 4.00 (d, 1H, *J* = 4.6 Hz), 2.81 (dd, 1H, *J* = 5.5, 16.1 Hz), 2.57 (ddd, 1H, *J* = 7.0, 11.8, 16.0 Hz), 2.21 (dd, 1H, *J* = 2.1, 11.7 Hz), 1.91 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H); m/z 300 [M+H]⁺.

Compound 68: Compound **27** (2.6 g, 9.0 mmol) was taken up in CH₂Cl₂, and 1,3-dibromo-5,5-dimethylhydantoin (1.7 g, 5.9 mmol) was added. The mixture was stirred for 3 h at room temperature. The reaction mixture was washed with 1N Na₂CO₃, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 35 % EtOAc in Hexanes) to give compound **68** (1.8 g, 54%) as a gummy solid. m/z 369, 371 (1:1) [M+H]⁺.

Compound 69: A mixture of Compound **68** (1.3 g, 3.5 mmol), phenylboronic acid (645 mg, 5.3 mmol), Ph₃P (190 mg, 0.73 mmol), K₃PO₄ (2.24 g, 10.6 mmol) and DME (15 mL) was sparged with N₂ for 10 min. Pd(OAc)₂ (80 mg, 0.35 mmol) was added and sparging with N₂ was continued for 10 min. The reaction was heated to 85 °C for 9 h. The reaction mixture was filtered and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 30 % EtOAc in Hexanes) to give compound **69** (0.69 g, 53%) as an off-white solid. m/z 367 [M+H]⁺.

Compound 70: Compound **69** (0.69 g, 1.9 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. Reaction mixture was extracted with ethyl acetate (2 × 25 mL) and washed saturated NaHCO₃, then dried with MgSO₄ and concentrated to give compound **70** (0.64 g, quantitative) as a solid. m/z 323 [M+H]⁺.

Compound 71: Compound **70** (0.64 g, 1.9 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted

with KH_2PO_4 (aq), extracted with ethyl acetate (2×25 mL) and washed with brine, then dried with MgSO_4 and concentrated to give compound **71** (0.61 g, 92%) as a solid. m/z 351 $[\text{M}+\text{H}]^+$.

Compound 72: A mixture of hydroxylamine hydrochloride and **71** (0.61 g, 1.7 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with ethyl acetate, then dried with MgSO_4 and concentrated to give compound **72** (0.58 g, 96%) as a solid. m/z 348 $[\text{M}+\text{H}]^+$.

Compound 73: Compound **72** (0.58 g, 1.7 mmol) was dissolved in a 1/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH_2PO_4 . The mixture was extracted with ethyl acetate and washed with brine, then dried with MgSO_4 and concentrated to give compound **73** (435 mg, 75%) as a solid. m/z 348 $[\text{M}+\text{H}]^+$.

Compound TX63465: Compound **73** (435 mg, 1.25 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 30 % EtOAc in Hexanes) to give compound **TX63465** (0.3 g, 69%) as a solid. ^1H NMR (400 MHz, d_6 -DMSO) δ 8.51 (s, 1H), 7.51 (m, 2H), 7.44 (s, 3H), 3.76 (s, 3H), 2.55 (m, 2H), 2.23 (d, 1H, $J = 11.9$ Hz), 1.89 (dd, 1H, $J = 5.0, 12.6$ Hz), 1.82 (m, 1H), 1.46 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); m/z 346 $[\text{M}+\text{H}]^+$.

Table 2. Compounds 74a-74l (Scheme 16).

Compound Name	R	Aryl boronic acid (1.5 eq)	$\text{Pd}(\text{OAc})_2$	DME (mL)	Yield (%)
74a	3-Cl	1.1 mmol	0.1 eq.	3.1	78
74b	4-Cl	1.1 mmol	0.1 eq.	3.1	68
74c	2-Cl	1.1 mmol	0.1 eq.	3.1	78
74d	3-F	0.57 mmol	0.3 eq	6	74
74e	4-F	0.58 mmol	0.3 eq	6	70

Compound Name	R	Aryl boronic acid (1.5 eq)	Pd(OAc) ₂	DME (mL)	Yield (%)
74f	2-Me	0.8 mmol	0.1 eq.	2.3	64
74g	2-OMe	1.1 mmol	0.1 eq.	3.1	69
74h	3-Me	0.60 mmol	0.3 eq	6	67
74i	3-OMe	0.61 mmol	0.3 eq	6	58
74j	4-Me	0.73 mmol	0.1 eq.	2.1	70
74k	4-OMe	1.1 mmol	0.1 eq.	3.1	48
74l	2-F	0.93 mmol	0.1 eq.	2.6	71

General method A: Compound **68** (1.0 eq.) was taken up in DME (See Table 2 for the amount). PhB(OH)₂ (See Table 2 for the amount), Ph₃P (0.2 eq.) and K₃PO₄ (3.0 eq.) were added, and the mixture was bubbled with N₂ for 10 min. Pd(OAc)₂ (See Table 2 for the amount) was added and the mixture was bubbled with N₂ for 10 min.

5 Then the mixture was stirred at 85 °C for 9 h. The reaction mixture was filtered, concentrated. The crude residue was purified by column chromatography to give the corresponding derivatives:

- Compound 74a:** 0.23g, 78%: m/z 401, 403 (3:1) [M+H]⁺.
- Compound 74b:** 0.2g, 68%: m/z 401, 403 (3:1) [M+H]⁺.
- 10 **Compound 74c:** 0.23g, 78%: m/z 401, 403 (3:1) [M+H]⁺.
- Compound 74d:** 0.1051g, 74%: m/z 385 [M+H]⁺.
- Compound 74e:** 0.0992g, 70%: m/z 385 [M+H]⁺.
- Compound 74f:** 0.13g, 64%: m/z 381 [M+H]⁺.
- Compound 74g:** 0.2g, 69%: m/z 397 [M+H]⁺.
- 15 **Compound 74h:** 0.097g, 67%: m/z 381 [M+H]⁺.
- Compound 74i:** 0.0872g, 58%: m/z 397 [M+H]⁺.
- Compound 74j:** 0.13g, 70%: m/z 381 [M+H]⁺.
- Compound 74k:** 0.14g, 48%: m/z 397 [M+H]⁺.
- Compound 74l:** 0.17g, 71%: m/z 385 [M+H]⁺.

Table 3. Compounds 75a-75l (Scheme 16).

Compound Name	R	74 (mmol) (starting materials)	HCl	MeOH (mL)	Yield (%)
75a	3-Cl	0.57	3N, 0.9 mL	1.5	quantitative
75b	4-Cl	0.5	3N, 0.4 mL	1.35	quantitative
75c	2-Cl	0.50	3N, 0.4 mL	1.35	quantitative
75d	3-F	0.27	1N, 1.6 mL	16.2	87
75e	4-F	0.26	1N, 1.6 mL	15.6	83
75f	2-Me	0.34	3N, 0.27 mL	0.92	quantitative
75g	2-OMe	0.50	3N, 0.4 mL	1.35	quantitative
75h	3-Me	0.255	1N, 1.5 mL	15.3	96
75i	3-OMe	0.22	1N, 1.3 mL	13.2	92
75j	4-Me	0.34	3N, 0.27 mL	0.92	quantitative
75k	4-OMe	0.35	3N, 0.28 mL	0.95	97
75l	2-F	0.44	3N, 0.35 mL	1.2	quantitative

General method B: Compound **74** (See Table 3 for the amount) was taken up in methanol (See Table 3 for the amount), and HCl (aq, See Table 3 for the amount) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted with ethyl acetate and washed with saturated NaHCO₃ (aq), then dried with MgSO₄ and concentrated to give the corresponding derivatives:

Compound 75a: 210 mg, quantitative: m/z 357, 359 (3:1) [M+H]⁺.

Compound 75b: 180 mg, quantitative: m/z 357, 359 (3:1) [M+H]⁺.

Compound 75c: 180 mg, quantitative: m/z 357, 359 (3:1) [M+H]⁺.

Compound 75d: 80.3 mg, 87%: m/z 341 [M+H]⁺.

Compound 75e: 79.7 mg, 83%: m/z 341 [M+H]⁺.

Compound 75f: 120 mg, quantitative: m/z 337 [M+H]⁺.

Compound 75g: 180 mg, quantitative: m/z 353 [M+H]⁺.

Compound 75h: 82.4 mg, 96%: m/z 337 [M+H]⁺.

Compound 75i: 71.5 mg, 92%: m/z 353 [M+H]⁺.

Compound 75j: 120 mg, quantitative: m/z 337 [M+H]⁺.

Compound 75k: 120 mg, 97%: m/z 353 [M+H]⁺.

Compound 75l: 150 mg, quantitative: m/z 341 [M+H]⁺.

Table 4. Compounds 76a-76l (Scheme 16).

Compound Name	R	75 (mmol) (starting materials)	HCO ₂ Et (mL)	MeONa (23% _{w/w} , eq)	Yield (%)
76a	3-Cl	0.588	4.7	10	97
76b	4-Cl	0.5	4	10	94
76c	2-Cl	0.5	4	10	94
76d	3-F	0.236	3.9	23.7	quantitative
76e	4-F	0.234	3.9	23.7	91
76f	2-Me	0.356	2.8	10	96
76g	2-OMe	0.51	4.1	10	93
76h	3-Me	0.245	4.1	23.7	quantitative
76i	3-OMe	0.20	3.3	23.7	quantitative
76j	4-Me	0.356	2.8	10	92
76k	4-OMe	0.34	2.7	10	97
76l	2-F	0.44	3.5	10	92

General method C: Compound **75** (See Table 4 for the amount) was taken up in ethyl formate (See Table 4 for the amount), and 30% NaOMe in methanol (See Table 4 for the amount) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with KH₂PO₄ (aq), then dried with MgSO₄ and concentrated to give the corresponding derivatives:

Compound 76a: 220 mg, 97%: m/z 385, 387 (3:1) [M+H]⁺.

Compound 76b: 180 mg, 94%: m/z 385, 387 (3:1) [M+H]⁺.

Compound 76c: 180 mg, 94%: m/z 385, 387 (3:1) [M+H]⁺.

Compound 76d: 93 mg, quantitative: m/z 369 [M+H]⁺.

Compound 76e: 77.8 mg, 91%: m/z 369 [M+H]⁺.

Compound 76f: 125 mg, 96%: m/z 365 [M+H]⁺.

Compound 76g: 180 mg, 93%: m/z 381 [M+H]⁺.

Compound 76h: 90.2 mg, quantitative: m/z 365 [M+H]⁺.

Compound 76i: 75.8 mg, 99.6%: m/z 381 [M+H]⁺.

5 **Compound 76j:** 120 mg, 92%: m/z 365 [M+H]⁺.

Compound 76k: 125 mg, 97%: m/z 381 [M+H]⁺.

Compound 76l: 150 mg, 92%: m/z 369 [M+H]⁺.

Table 5. Compounds 77a-77l (Scheme 16).

Compound Name	R	76 (mmol) (starting materials)	NH ₂ OH·HCl (eq)	Yield (%)
77a	3-Cl	0.57	2	quantitative
77b	4-Cl	0.47	2	quantitative
77c	2-Cl	0.47	2	quantitative
77d	3-F	0.29	1.1	92
77e	4-F	0.21	1.1	94
77f	2-Me	0.34	2	quantitative
77g	2-OMe	0.47	2	95
77h	3-Me	0.25	1.1	94
77i	3-OMe	0.20	1.1	87
77j	4-Me	0.33	2	quantitative
77k	4-OMe	0.33	2	quantitative
77l	2-F	0.41	2	quantitative

General method D: A solution of 0.1 N hydroxylamine hydrochloride (aq, See Table 5 for the amount) was added to compound **76** (See Table 5 for the amount). A 9/1 mixture of ethanol/water was added, and 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 dried with MgSO₄ and concentrated to give the corresponding derivatives:

15 **Compound 77a:** 220 mg, quantitative: m/z 382, 384 (3:1) [M+H]⁺.

Compound 77b: 180 mg, quantitative: m/z 382, 384 (3:1) [M+H]⁺.

Compound 77c: 180 mg, quantitative: m/z 382, 384 (3:1) [M+H]⁺.

Compound 77d: 84 mg, 92%: m/z 366 [M+H]⁺.

Compound 77e: 72.1 mg, 94%: m/z 366 [M+H]⁺.

Compound 77f: 125 mg, quantitative: m/z 362 [M+H]⁺.

Compound 77g: 170 mg, 95%: m/z 378 [M+H]⁺.

Compound 77h: 84.0 mg, 94%: m/z 362 [M+H]⁺.

Compound 77i: 66.0 mg, 87%: m/z 378 [M+H]⁺.

5 **Compound 77j:** 125 mg, quantitative: m/z 362 [M+H]⁺.

Compound 77k: 130 mg, quantitative: m/z 378 [M+H]⁺.

Compound 77l: 150 mg, quantitative: m/z 366 [M+H]⁺.

Table 6. Compounds 78a-78l (Scheme 16).

Compound Name	R	81 (mmol) (starting materials)	MeONa (30% _{w/w} , eq)	Yield (%)
78a	3-Cl	0.58	8	quantitative
78b	4-Cl	0.47	8	95
78c	2-Cl	0.47	8	quantitative
78d	3-F	0.23	20	quantitative
78e	4-F	0.20	20	quantitative
78f	2-Me	0.35	8	96
78g	2-OMe	0.45	8	quantitative
78h	3-Me	0.23	20	86
78i	3-OMe	0.17	20	quantitative
78j	4-Me	0.35	8	88
78k	4-OMe	0.34	8	quantitative
78l	2-F	0.41	8	quantitative

General method E: Compound 77 (See Table 6 for the amount) was dissolved in a 3/1 methanol/THF mixture, and 30% Sodium methoxide (See Table 6 for the amount) was added, and the reaction mixture was stirred at 55 °C for 5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give the corresponding derivatives:

Compound 78a: 220 mg, quantitative: m/z 382, 384 (3:1) [M+H]⁺.

Compound 78b: 170 mg, 95%: m/z 382, 384 (3:1) [M+H]⁺.

Compound 78c: 180 mg, quantitative: m/z 382, 384 (3:1) [M+H]⁺.

Compound 78d: 88 mg, quantitative: m/z 366 [M+H]⁺.

Compound 78e: 93.4 mg, quantitative: m/z 366 [M+H]⁺.

Compound 78f: 120 mg, 96%: m/z 362 [M+H]⁺.

Compound 78g: 170 mg, quantitative: m/z 378 [M+H]⁺.

5 **Compound 78h:** 71.5 mg, 86%: m/z 362 [M+H]⁺.

Compound 78i: 72.0 mg, quantitative: m/z 378 [M+H]⁺.

Compound 78j: 110 mg, 88%: m/z 362 [M+H]⁺.

Compound 78k: 130 mg, quantitative: m/z 378 [M+H]⁺.

Compound 78l: 150 mg, quantitative: m/z 366 [M+H]⁺.

10 **Table 7. Compounds of Scheme 16.**

Compound Name	R	82 (mmol) (starting materials)	DBDMH (eq)	Pyridine (eq)	Yield (%)
TX63485	3-Cl	0.58	0.55	10	57
TX63486	4-Cl	0.45	0.55	10	53
TX63491	2-Cl	0.47	0.55	10	67
TX63506	3-F	0.24	0.64	9.4	26
TX63507	4-F	0.20	0.64	9.4	37
TX63508	2-Me	0.33	0.55	10	34
TX63509	2-OMe	0.45	0.55	10	21
TX63512	3-Me	0.20	0.64	9.4	31
TX63513	3-OMe	0.19	0.64	9.4	24
TX63514	4-Me	0.30	0.55	10	55
TX63515	4-OMe	0.34	0.55	10	39
TX63519	2-F	0.41	0.55	10	50

General method F: Compound **78** (See Table 7 for the amount) was dissolved in dry DMF, and the solution was cooled to 0 °C. Dibromodimethylhydantoin (See Table 7 for the amount) was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine (See Table 7 for the amount) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column

chromatography (silica gel, 25 % EtOAc in Hexanes) to give the corresponding derivatives:

TX63485: 125 mg, 57%: ^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1H), 7.20-7.48 (m, 4H), 3.81 (s, 3H), 2.68 (dd, 1H, $J = 12.0, 4.0$ Hz), 2.51-2.61 (m, 1H), 2.24 (d, 1H, $J = 8.0$ Hz), 1.82-1.99 (m, 2H), 1.55 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); m/z 380, 382 (3:1) $[\text{M}+\text{H}]^+$.

TX63486: 89 mg, 53%: ^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1H), 7.48 (d, 2H, $J = 8.0$ Hz), 7.28 (d, 2H, $J = 8.0$ Hz), 3.80 (s, 3H), 2.66 (dd, 1H, $J = 12.0, 4.0$ Hz), 2.50-2.60 (m, 1H), 2.24 (dd, 1H, $J = 12.0, 2.0$ Hz), 1.82-1.99 (m, 2H), 1.55 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); m/z 380, 382 (3:1) $[\text{M}+\text{H}]^+$.

TX63491: 120 mg, 67%: ^1H NMR (500 MHz, CDCl_3) δ 8.56 (s, 1H), 7.55 (m, 1H), 7.45 (m, 1H), 7.45-7.25 (m, 2H), 3.67 (s, 3H), 2.60-2.39 (m, 2H), 2.29-2.20 (m, 1H), 1.91-1.85 (m, 2H), 1.60 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); m/z 380, 382 (3:1) $[\text{M}+\text{H}]^+$.

TX63506: 22.5 mg, 26%: ^1H NMR (400 MHz, CDCl_3) δ 8.54 (s, 1H), 7.45-7.52 (m, 1H), 7.10-7.18 (m, 2H), 7.04-7.08 (m, 1H), 3.83 (s, 3H), 2.69 (dd, 1H, $J = 12.0, 4.0$ Hz), 2.52-2.62 (m, 1H), 2.24 (d, 1H, $J = 8.0$ Hz), 1.83-1.98 (m, 2H), 1.55 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); m/z 364 $[\text{M}+\text{H}]^+$.

TX63507: 26.9 mg, 37%: ^1H NMR (400 MHz, CDCl_3) δ 8.54 (s, 1H), 7.16-7.28 (m, 2H), 7.28-7.30 (m, 2H), 3.79 (s, 3H), 2.66 (dd, 1H, $J = 12.0, 4.0$ Hz), 2.49-2.58 (m, 1H), 2.24 (dd, 1H, $J = 8.0, 2.0$ Hz), 1.82-1.97 (m, 2H), 1.55 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); m/z 364 $[\text{M}+\text{H}]^+$.

TX63508: 40 mg, 34%: ^1H NMR (400 MHz, DMSO) δ 8.52 (s, 1H), 7.16-7.45 (m, 4H), 7.06 (d, 2H, $J = 8.0$ Hz), 3.82 (s, 3H), 3.74 (s, 3H), 2.45-2.60 (m, 2H), 2.22 (d, 1H, $J = 8.0$ Hz), 1.75-1.93 (m, 2H), 1.45 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); m/z 360 $[\text{M}+\text{H}]^+$.

TX63509: 35 mg, 21%: ^1H NMR (500 MHz, CDCl_3) δ 8.57 (s, 1H), 7.45 (m, 1H), 7.23-7.18 (m, 1H), 7.08-7.03 (m, 2H), 3.85 (br s, 3H), 3.69 (s, 3H), 2.58-2.52 (m, 1H), 2.27 (m, 1H), 1.89 (m, 2H), 1.57 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H); m/z 376 $[\text{M}+\text{H}]^+$.

TX63512: 22.2 mg, 31%: ^1H NMR (400 MHz, CDCl_3) δ 8.55 (s, 1H), 7.38 (t, 1H, $J = 4.0$ Hz), 7.10-7.31 (m, 3H), 3.81 (s, 3H), 2.68 (dd, 1H, $J = 12.0, 4.0$ Hz),

2.53-2.62 (m, 1H), 2.44 (s, 3H), 2.25 (dd, 1H, $J = 8.0, 2.0$ Hz), 1.82-1.96 (m, 2H), 1.55 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); m/z 360 $[M+H]^+$.

TX63513: 17.1 mg, 24%: ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.43 (t, 1H, $J = 12.0$ Hz), 6.85-7.01 (m, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 2.70 (dd, 1H, $J = 12.0, 4.0$ Hz), 2.52-2.62 (m, 1H), 2.25 (dd, 1H, $J = 12.0, 2.0$ Hz), 1.82-1.98 (m, 2H), 1.56 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); m/z 376 $[M+H]^+$.

TX63514: 60 mg, 55%: ^1H NMR (400 MHz, DMSO) δ 8.50 (s, 1H), 7.29-7.38 (m, 4H), 3.75 (s, 3H), 2.47-2.62 (m, 2H), 2.37 (s, 3H), 2.23 (d, 1H, $J = 12.0$ Hz), 1.76-1.93 (m, 2H), 1.45 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); m/z 381 $[M+H]^+$.

TX63515: 50 mg, 39%: ^1H NMR (400 MHz, DMSO) δ 8.50 (s, 1H), 7.38 (d, 2H, $J = 8.0$ Hz), 7.06 (d, 2H, $J = 8.0$ Hz), 3.82 (s, 3H), 3.74 (s, 3H), 2.45-2.60 (m, 2H), 2.22 (d, 1H, $J = 8.0$ Hz), 1.75-1.93 (m, 2H), 1.45 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); m/z 376 $[M+H]^+$.

TX63519: 75 mg, 50%: ^1H NMR (500 MHz, d_6 -DMSO) δ 8.51 (s, 1H), 7.56 (m, 1H), 7.49 (m, 1H), 7.43-7.34 (m, 2H), 3.68 (s, 3H), 2.45 (m, 1H), 2.23 (m, 1H), 1.84 (m, 2H), 1.47 (s, 3H), 1.25 (s, 3H), 1.14 (s, 3H); m/z 364 $[M+H]^+$.

Compound 79a: A mixture of Compound **68** (270 mg, 0.73 mmol), 3-pyridinylboronic acid (1.5 equiv.), Ph_3P (0.2 equiv.), K_3PO_4 (3.0 equiv.) and DME was sparged with N_2 for 10 min. $Pd(OAc)_2$ (0.1 equiv.) was added and sparging with N_2 was continued for 10 min. The reaction was heated to 85 °C for 9 h. The reaction mixture was filtered and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 30 % EtOAc in Hexanes) to give compound **79a** (70 mg, 26%) as a solid. m/z 368 $[M+H]^+$.

Compound 79b: Compound **68** (290 mg, 0.79 mmol) was reacted with 4-pyridinylboronic acid employing the same procedure used to produce **79a** to give **79b** (140 mg, 49%) as a solid. m/z 368 $[M+H]^+$.

Compound 80a: Compound **79a** (70 mg, 0.19 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The reaction mixture was extracted with ethyl acetate (2×25 mL) and washed saturated $NaHCO_3$, then dried with $MgSO_4$ and concentrated to give compound **80a** (60 mg, 97%) as a solid. m/z 324 $[M+H]^+$.

Compound 80b: Compound **79b** (140 mg, 0.38 mmol) was subjected to the same procedure used to prepare **80a** to give **80b** (130 mg, quantitative) as a solid. m/z 324 $[M+H]^+$.

5 **Compound 81a:** Compound **80a** (60 mg, 0.19 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH_2PO_4 (aq), extracted with ethyl acetate (2×25 mL) and washed with brine, then dried with $MgSO_4$ and concentrated to give compound **81a** (70 mg, quantitative) as a solid. m/z 352 $[M+H]^+$.

10 **Compound 81b:** Compound **80b** (130 mg, 0.38 mmol) was subjected to the same procedure used to prepare **81a** to give **81b** (135 mg, quantitative) as a solid. m/z 352 $[M+H]^+$.

Compound 82a: A mixture of hydroxylamine hydrochloride and **81a** (70 mg, 0.19 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room
15 temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with ethyl acetate, then dried with $MgSO_4$ and concentrated to give compound **82a** (70 mg, quantitative) as a solid. m/z 349 $[M+H]^+$.

Compound 82b: Compound **81b** (135 mg, 0.38 mmol) was subjected to the same procedure used to prepare **82a** to give **82b** (135 mg, quantitative) as a solid. m/z
20 349 $[M+H]^+$.

Compound 83a: Compound **82a** (70 mg, 0.19 mmol) was dissolved in a 1/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH_2PO_4 . The mixture was
25 extracted with ethyl acetate and washed with brine, then dried with $MgSO_4$ and concentrated to give compound **83a** (70 mg, quantitative) as a solid. m/z 349 $[M+H]^+$.

Compound 83b: Compound **82b** (135 mg, 0.38 mmol) was subjected to the same procedure used to prepare **83a** to give **83b** (135 mg, quantitative) as a solid. m/z 349 $[M+H]^+$.

30 **Compound TX63503:** Compound **83a** (65 mg, 0.19 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. Br_2 was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C

overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 35 % EtOAc in Hexanes with 0.5% Et₃N) to give compound **TX63503** (20 mg, 31%) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.69 (dd, 1H, *J* = 1.5, 4.8 Hz), 8.64 (d, 1H, *J* = 1.4 Hz), 8.53 (s, 1H), 7.69 (td, 1H, *J* = 1.8, 7.9 Hz), 7.46 (dd, 1H, *J* = 4.9, 7.3 Hz), 3.83 (s, 3H), 2.70 (dd, 1H, *J* = 4.8, 16.0 Hz), 2.58 (ddd, 1H, *J* = 6.8, 11.6, 15.9 Hz), 2.25 (dd, 1H, *J* = 1.9, 11.9 Hz), 1.92 (m, 2H), 1.56 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); *m/z* 347 [M+H]⁺.

Compound TX63505: Compound **83b** (135 mg, 0.38 mmol) was subjected to the same procedure used to prepare **TX63503** to give **TX63505** (35 mg, 27%) as a solid. ¹H NMR (400 MHz, *d*₆-DMSO) δ 8.71 (d, 2H, *J* = 4.6 Hz), 8.51 (s, 1H), 7.51 (d, 2H, *J* = 4.5 Hz), 3.85 (s, 3H), 2.63 (m, 2H), 2.24 (d, *J* = 12.0 Hz, 1H), 1.86 (m, 2H), 1.46 (s, 3H), 1.23 (s, 3H), 1.14 (s, 3H); *m/z* 347 [M+H]⁺.

Compound 84: Compound **18** (1.04 g, 4.64 mmol) was taken up in *t*-BuOH and added to a solution of KO*t*-Bu in *t*-BuOH. The reaction was stirred for 5 min at room temperature and 1,4-dibromobutane was added. The reaction was stirred at room temperature for 80 min, then warmed to 45 °C until the starting material was consumed, as reported by thin layer chromatography. The reaction mixture was concentrated, diluted with water, and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated. The crude residue was purified by column chromatography (silica gel, 10 % EtOAc in Hexanes) to give compound **84** (1.006 g, 78%) as an oil. *m/z* 279 [M+H]⁺.

Compound 85: Compound **84** (1.561 g, 5.61 mmol) was taken up in EtOH under N₂ and 20% Pd(OH)₂ added. The Parr shaker bottle was rigorously purged with H₂ and charged at 54 psi. The flask was shaken overnight at room temperature. The reaction mixture was filtered and concentrated. The crude residue was purified by column chromatography (silica gel 6 to 50 % EtOAc in Hexanes) to give compound **85** (0.493 g, 31%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 4.72 (d, 1H, *J* = 6.8 Hz), 4.59 (d, 1H, *J* = 6.8 Hz), 3.38 (s, 3H), 3.11 (dd, 1H, *J* = 4.2, 11.6 Hz), 2.76 (dt, 1H, *J* = 5.9, 15.0 Hz), 2.44 (td, 1H, *J* = 7.5, 13.0 Hz), 2.32 (td, 1H, *J* = 3.4, 15.0 Hz), 2.22 (ddd, 1H, *J* = 2.9, 5.8, 13.8 Hz), 1.87 (m, 2H), 1.79 (m, 1H), 1.69 (m, 1H), 1.50 (m, 8H), 1.30 (m, 3H), 1.12 (s, 3H).

Compound 86: A mixture of Compound **85** (460 mg, 1.64 mmol), ethylene glycol, and *p*-toluenesulfonic acid hydrate in toluene was heated to reflux overnight with azeotropic removal of water. The reaction mixture was cooled to room

temperature, diluted with EtOAc, washed with saturated NaHCO₃ and brined, then dried with MgSO₄ and concentrated to give compound **86** (497 mg, quantitative) as a solid. m/z 263 (M-H₂O+1).

Compound 87: Compound **86** (497 mg, 1.64 mmol) was taken up in CH₂Cl₂ and pyridinium dichromate was added over 10 min. The reaction mixture was stirred overnight at room temperature, then heated to 45 °C until the starting material was consumed, as reported by thin layer chromatography. The reaction mixture was filtered through Celite, eluted with CH₂Cl₂, and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give Compound **87** (359 mg, 73%) as a solid. m/z 279 [M+H]⁺.

Compound 88: Compound **87** (352 mg, 1.26 mmol) was taken up in ethyl formate and cooled to 0 °C, then 30% sodium methoxide (30 wt% solution in MeOH) was added and the reaction warmed to room temperature. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and the pH adjusted to 7 with acetic acid. The mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated to give compound **88** (384 mg, 99%) as a solid. m/z 307 [M+H]⁺.

Compound 89: A mixture of **88** (227 mg, 0.74 mmol) and methyl hydrazine (2.7 equiv.) in ethanol (100 mL) was stirred at room temperature for 2 h, then heated to 60 °C for 1 h. The reaction mixture was concentrated. The crude residue was triturated with ether/EtOAc to give **89** (176 mg, 75%) as a solid. m/z 317 [M+H]⁺.

Compound 90: Compound **89** (93 mg, 0.29 mmol) was taken up in methanol, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was concentrated, extracted with EtOAc and washed with saturated NaHCO₃ (aq), then dried with MgSO₄ and concentrated to give compound **90** (83 mg, quantitative) as a solid. m/z 273 [M+H]⁺.

Compound 91: Compound **90** (80 mg, 0.29 mmol) was taken up in ethyl formate and cooled to 0 °C, then 30% sodium methoxide (30 wt% solution in MeOH) was added and the reaction warmed to room temperature. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH₂PO₄ (aq), extracted with EtOAc, then dried with MgSO₄ and concentrated to give **91** (89 mg, quantitative) as a solid. m/z 301 [M+H]⁺.

Compound 92: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **91** (87 mg, 0.29 mmol). A 9/1 mixture of ethanol/water was

added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, then dried with MgSO₄ and concentrated to give compound **92** (83 mg, 96%) as a solid. m/z 298 [M+H]⁺.

5 **Compound 93:** Compound **92** (77 mg, 0.26 mmol) was dissolved in a 3/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄ (aq), and the reaction mixture was concentrated. The residue was extracted with
10 EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **93** (81 mg, quantitative) as a solid. m/z 298 [M+H]⁺.

Compound TX63487: Compound **93** (81 mg, 0.26 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin
15 was added, and the reaction stirred at 0 °C until the starting material was consumed, as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and
20 concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **TX63487** (29 mg, 38%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.07 (s, 1H), 3.87 (s, 3H), 2.78 (dd, 1H, *J* = 4.8, 14.9 Hz), 2.55 (ddd, 1H, *J* = 7.5, 11.6, 15.3 Hz), 2.33 (dd, 1H, *J* = 2.8, 10.9 Hz), 2.27 (m, 1H), 1.83 (m, 5H), 1.63 (m, 3H), 1.44 (s, 3H), 1.27 (m, 1H); m/z 296
25 [M+H]⁺.

Compound 94: Compound **89** (159 mg, 0.50 mmol) was taken up in CH₂Cl₂, and 1,3-dibromo-5,5-dimethylhydantoin was added. The mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated, diluted with EtOAc, washed with saturated NaHCO₃ (aq) and brine, then dried over MgSO₄ and
30 concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **94** (123 mg, 62%) as a solid. m/z 395, 397 (1:1) [M+H]⁺.

Compound 95: A mixture of Compound **94** (121 mg, 0.31 mmol), phenylboronic acid (56 mg, 0.46 mmol), Ph₃P (18 mg, 0.07 mmol), K₃PO₄ (210 mg,

0.99 mmol) and DME (10 mL) was sparged with N₂ for 10 min. Pd(OAc)₂ (16 mg, 0.07 mmol) was added and sparging with N₂ was continued for 10 min. The reaction was heated to 85 °C for 12 h. The reaction mixture was filtered through MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **95** (88 mg, 73%) as a white solid. m/z 393 [M+H]⁺.

Compound 96: Compound **95** (84 mg, 0.21 mmol) was taken up in methanol, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. Reaction mixture was extracted with ethyl acetate and washed saturated NaHCO₃, then dried with MgSO₄ and concentrated to give compound **96** (79 mg, quantitative) as a solid. m/z 349 [M+H]⁺.

Compound 97: Compound **96** (75 mg, 0.21 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with ethyl acetate and washed with KH₂PO₄ (aq), then dried with MgSO₄ and concentrated to give compound **97** (38 mg, 47%) as a solid. m/z 377 [M+H]⁺.

Compound 98: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **97** (38 mg, 0.10 mmol). A 9/1 mixture of ethanol/water was added, and 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 dried with MgSO₄ and concentrated to give compound **98** (38 mg, quantitative) as a solid. m/z 374 [M+H]⁺.

Compound 99: Compound **98** (38 mg, 0.10 mmol) was dissolved in a 3/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **99** (40 mg, quantitative) as a solid. m/z 374 [M+H]⁺.

Compound TX63504: Compound **99** (40 mg, 0.10 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed, as reported by thin layer chromatography. Then, pyridine was added, and the reaction

was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **TX63504** (14 mg, 37%) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 8.52 (s, 1H), 7.50 (t, 2H, *J* = 7.0 Hz), 7.44 (t, 1H, *J* = 6.7 Hz), 7.34 (d, 2H, *J* = 7.0 Hz), 3.82 (s, 3H), 2.67 (d, 1H, *J* = 6.2 Hz), 2.56 (m, 1H), 2.40 (d, 1H, *J* = 10.4 Hz), 2.28 (m, 1H), 1.84 (m, 5H), 1.65 (m, 3H), 1.50 (s, 3H), 1.28 (m, 1H); *m/z* 372 [M+H]⁺.

Compound 48 and 100: Compound **26** (100 mg, 0.36 mmol) was taken up in toluene (10 ml), sparged with N₂ for 5 min, and phenylhydrazine (381, 0.38 mmol) was added. The vial was sealed and the reaction stirred at 75 °C overnight. The reaction mixture was cooled to room temperature and concentrated. The residue was taken up in toluene (10 mL) and *p*-toluenesulfonic acid hydrate (12 mg, 0.06 mmol) was added, then the mixture was sparged with N₂ for 3 min. The reaction was stirred at 80 °C overnight, then at room temperature for 3 d. The reaction mixture was concentrated to give a mixture of compounds **48** and **100**: *m/z* 353 [M+H]⁺.

Compounds 50 and 101: The mixture of compounds **48** and **100** was taken up in methanol, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The reaction mixture was extracted with EtOAc (50 mL) and washed with saturated NaHCO₃, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 10 to 25 % EtOAc in Hexanes) to give compound **50** (19 mg, 17%) and compound **101** (57.1 mg, 52%) as solids: *m/z* 309 [M+H]⁺.

Compound 102: Compound **101** (50.4 mg, 0.16 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH₂PO₄ (aq) and extracted with EtOAc, then dried with MgSO₄ and concentrated to give compound **102** (61.4 mg, quantitative) as a solid. *m/z* 337 [M+H]⁺.

Compound 103: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **102** (61.4 mg, 0.16 mmol). A 9/1 mixture of ethanol/water was added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in

EtOAc, then dried with MgSO_4 and concentrated to give compound **103** (48.5 mg, 89%) as a solid. m/z 334 $[\text{M}+\text{H}]^+$.

Compound 104: Compound **103** (47.5 mg, 0.14 mmol) was dissolved in a 3/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The reaction mixture was stirred at 55 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 , and the reaction mixture was concentrated. The residue was extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **104** (42.5 mg, 89%) as a solid. m/z 334 $[\text{M}+\text{H}]^+$.

Compound TX63524: Compound **104** (42.5 mg, 0.13 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc/Hexanes) to give compound **TX63524** (11.8 mg, 28%) as a solid. ^1H NMR (500 MHz, CDCl_3) δ 7.60 (m, 3H), 7.57 (s, 1H), 7.46 (s, 1H), 7.45 (m, 2H), 2.86 (ddd, 1H, $J = 1.1, 5.7, 15.9$ Hz), 2.65 (ddd, 1H, $J = 6.7, 12.0, 16.1$ Hz), 2.32 (dd, 1H, $J = 1.9, 11.9$ Hz), 1.95 (m, 2H), 1.60 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H); m/z 332 $[\text{M}+\text{H}]^+$.

Compound 105: Compound **26** (0.282 g, 1.0 mmol) was taken up in 0.1 M hydroxylamine hydrochloride in 9:1 EtOH/ H_2O (11 mL, 1.1 mmol) and triethylamine (0.15 mL, 1.1 mmol) was added. The mixture was stirred at room temperature for 15 minutes. The reaction mixture was briefly warmed to 45 °C and was stirred overnight at room temperature. The mixture was heated to 60 °C briefly to ensure cyclization and was then concentrated, diluted with EtOAc, dried over MgSO_4 , filtered and concentrated to a glass. m/z $[\text{M}+\text{H}]^+$ 278.1

To a solution of the above intermediate (305 mg, 1.1 mmol) in THF and MeOH (2:1), 30% NaOMe (8 eq) was added, and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with KH_2PO_4 (sat.) and extracted with EtOAc. The combined organic extracts were washed with brine, dried

with MgSO_4 , and concentrated in vacuo to give **105** (0.297 g). m/z $[\text{M}+\text{H}]^+$ 278.1. This material was used directly in the next step.

Compound 106: Compound **105** (0.297 g, 1.1 mmol) was taken up in EtOH (20 mL) and methylhydrazine (0.15 g, 3.26 mmol) was added as a solution in EtOH (1 mL) dropwise at room temperature. The reaction was heated overnight and six additional hours at reflux. The reaction mixture was cooled and concentrated. The residue was chromatographed on silica gel (230–400 mesh, 18 g) using 3:1, then 1:1, Hexanes/EtOAc as eluant. Compound **106** (62 mg, 18%) was obtained as a glass. m/z $[\text{M}+\text{H}]^+$ 306.2.

Compound 107: Compound **106** (0.062 g, 0.20 mmol) was dissolved in EtOAc (7 mL). Triethylamine (0.06 mL, 0.4 mmol) was added followed by addition of benzoyl chloride (0.069 g, 0.49 mmol) and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with EtOAc (50 mL), washed with saturated aqueous NaHCO_3 solution (10 mL), dried over MgSO_4 , filtered and concentrated to a dark oil to afford **107** (0.1145 g) which was used without further purification. m/z $[\text{M}+\text{H}]^+$ 410.3.

Compound 108: A solution of **107** (114.5 mg, 0.28 mmol) in MeOH (5 mL) was treated with 3N HCl (aq), stirred at room temperature overnight. The reaction mixture was concentrated, extracted with EtOAc (2×25 mL) and sat'd NaHCO_3 (aq). The organic layer was dried with MgSO_4 , concentrated to give **108** (57 mg, 57%). m/z $[\text{M}+\text{H}]^+$ 366.2.

Compound 109: To a solution of **108** (57 mg, 0.16 mmol) in 2 mL of HCOOEt at RT, 30% NaOMe in MeOH (6 eq) was added dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat. KH_2PO_4 solution. The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , and concentrated in vacuo to give **109** (63 mg) which was used without further purification. m/z $[\text{M}+\text{H}]^+$ 394.2.

Compound 110: To a solution of **109** (0.063 g, 0.16 mmol) in 2 mL of EtOH, $\text{NH}_2\text{OH} \cdot \text{HCl}$ salt (2 eq) was added, and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried with MgSO_4 , and concentrated in vacuo to give **110** (0.0613 g) which was used without further purification. m/z $[\text{M}+\text{H}]^+$ 391.2.

Compound 111: To a solution of Compound **110** (0.0613 g, 0.16 mmol) in THF and MeOH (2:1), 30% NaOMe (8 eq) was added, and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with KH₂PO₄ (sat.) and extracted with EtOAc. The combined organic extracts were washed with
5 brine, dried with MgSO₄, and concentrated in vacuo to give **111** (0.0493 g) which was used without further purification. *m/z* [M+H]⁺ 391.2.

Compound TX63531: To a solution of **111** (0.0493 g, 0.13 mmol) in 1 mL of DMF at 0 °C, 1,3-Dibromo-5,5-dimethylhydantoin (0.55 eq) was added, and the solution was stirred for 2 hours. Pyridine (30 eq) was added, and the solution was
10 heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 2:1 DCM/EtOAc to give **TX63531** (5.8 mg, 11%). ¹H NMR (500 MHz, CDCl₃) δ 8.44 (s, 1H), 7.88 (d, 2H, *J* = 4.3 Hz), 7.60 (t, 1H, *J* = 5.6 Hz), 7.54 (br s, 1H), 7.51 (m, 2H), 3.73 (s, 3H), 2.60 (m, 1H), 2.44 (m, 1H), 2.14 (d, 1H, *J* = 8.8 Hz), 1.79–1.66 (m, 2H), 1.49 (s, 3H), 1.36 (s, 3H), 1.07 (s, 3H); *m/z*
15 [M+H]⁺ 389.2.

Compound TX63524: Compound **104** (42.5 mg, 0.13 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine
20 was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25 % EtOAc in Hexanes) to give compound **TX63524** (11.8 mg, 28%) as a
25 solid. ¹H NMR (500 MHz, CDCl₃) δ 7.60 (m, 3H), 7.57 (s, 1H), 7.46 (s, 1H), 7.45 (m, 2H), 2.86 (ddd, 1H, *J* = 1.1, 5.7, 15.9 Hz), 2.65 (ddd, 1H, *J* = 6.7, 12.0, 16.1 Hz), 2.32 (dd, 1H, *J* = 1.9, 11.9 Hz), 1.95 (m, 2H), 1.60 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H). *m/z* 332 [M+H]⁺.

Compound 112: A solution of **17** (6.4 g, 36 mmol) in THF (25 mL) was
30 added to a -78 °C solution of lithium (2 equiv.) in liq. NH₃ (10 mL). The reaction was stirred at -78 °C for 45 min, quenched with NH₄Cl (10 g), and warmed to room temperature. The mixture was diluted with water, extracted with EtOAc, and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **112** (1.5 g, 23%) as an oil. *m/z* 183 [M+H]⁺.

Compound 113: A mixture of Compound **112** (1.5 g, 8.2 mmol), ethylene glycol, and *p*-toluenesulfonic acid hydrate in benzene was heated to reflux for 4 h with azeotropic removal of water. The reaction mixture was cooled to room temperature, washed with water, and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **113** (1.4 g, 75%) as an oil. m/z 227 $[M+H]^+$.

Compound 114: Compound **113** (1.4 g, 6.2 mmol) was taken up in CH_2Cl_2 (100 mL), then $MgSO_4$ (150 mg) and PDC (2 equiv.) were added. The reaction was stirred at room temperature for 2 d. The reaction mixture was filtered through a pad of silica (eluted with CH_2Cl_2) and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **114** (1.25 g, 90%) as a white solid. m/z 225 $[M+H]^+$.

Compound 115: Compound **114** (1.25 g, 5.57 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched KH_2PO_4 (aq) and extracted with EtOAc, then washed with water, dried with $MgSO_4$ and concentrated to give compound **115** (1.35 g, 96%) as a solid. m/z 253 $[M+H]^+$.

Compound 116: A mixture of compound **115** (1.35 g, 5.35 mmol) and methyl hydrazine (1.6 equiv.) in ethanol was heated to 60 °C for 2 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, EtOAc) to give **116** (1.2 g, 85%) as a solid. m/z 263 $[M+H]^+$.

Compound 117: Compound **116** (1.2 g, 4.6 mmol) was taken up in CH_2Cl_2 and 1,3-dibromo-5,5-dimethylhydantoin (0.55 equiv.) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was washed with 1 N Na_2CO_3 and concentrated. The crude residue was purified by column chromatography (silica gel, 10 to 30 % EtOAc in Hexanes) to give **117** (1.0 g, 64%) as a solid. m/z 341, 343 (1:1) $[M+H]^+$.

Compound 118: A mixture of Compound **117** (1.0 g, 2.9 mmol), phenylboronic acid (1.25 equiv.), Ph_3P (0.3 equiv.), K_3PO_4 (3 equiv.) and DME was sparged with N_2 for 10 min. $Pd(OAc)_2$ (0.15 equiv.) was added and sparging with N_2 was continued for 10 min. The reaction was heated to 85 °C for 16 h. The reaction mixture was filtered and concentrated. The crude residue was purified by column

chromatography (silica gel, 10 to 30 % EtOAc in Hexanes) to give compound **118** (0.53 g, 53%) as an oil. m/z 339 $[M+H]^+$.

Compound 119: Compound **118** (0.53 g, 1.6 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The reaction mixture was diluted with saturated NaHCO_3 and extracted with EtOAc (2×25 mL), then dried with MgSO_4 and concentrated to give compound **119** (0.42 g, 91%) as a solid. m/z 295 $[M+H]^+$.

Compound 120: Compound **119** (0.42 g, 1.4 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched KH_2PO_4 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 and concentrated to give compound **120** (0.44 g, 96%) as a solid. m/z 323 $[M+H]^+$.

Compound 121: A mixture of hydroxylamine hydrochloride and **120** (0.44 g, 1.4 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **121** (445 mg, quantitative) as a solid. m/z 320 $[M+H]^+$.

Compound 122: Compound **121** (445 mg, 1.4 mmol) was dissolved in a 1/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH_2PO_4 . The mixture was extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated to give compound **122** (440 mg, quantitative) as a solid. m/z 320 $[M+H]^+$.

Compound TX63540: Compound **122** (440 mg, 1.4 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 15 to 35 %

EtOAc in Hexanes) to give compound **TX63540** (120 mg, 28%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.55 (s, 1H), 7.50 (t, 2H, $J = 8.1$ Hz), 7.45 (m, 1H), 7.35 (d, 2H, $J = 8.0$ Hz), 3.83 (s, 3H), 2.64 (m, 4H), 2.51 (ddt, 1H, $J = 1.7, 5.7, 12.3$ Hz), 1.89 (m, 1H), 1.77 (m, 1H), 1.48 (s, 3H); m/z 318 $[\text{M}+\text{H}]^+$.

5 **Compound 123:** Compound **1** (30.0 g, 238 mmol) was suspended in acetonitrile and the mixture cooled to 0 °C. Ethyl vinyl ketone (25 g, 297 mmol) and triethyl amine (53 ml, 380 mmol) were added and the reaction was warmed to room temperature and stirred overnight. The reaction mixture was concentrated. The residue was taken up in EtOAc and washed with KH_2PO_4 (aq) and brine, then dried
10 with MgSO_4 and concentrated. The residue was taken up in benzene (250 mL), pyrrolidine (5.0 ml, 60 mmol) was added, and the reaction was heated to reflux for 48 h with azeotropic removal of water. The reaction mixture was cooled to room temperature and concentrated. The residue was taken up in EtOAc, washed with saturated NaHCO_3 and brine, then dried with MgSO_4 and concentrated. The crude
15 residue was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to give a yellow oil. The oil was crystallized from cold *t*-BuOMe (50 mL) to give **123** (18.59 g, 41%) as a white solid.

Compound 124: A solution of NaBH_4 (0.64 g, 17 mmol) in ethanol (100 mL) was added to a 0 °C solution of compound **123** (12.97 g, 67.5 mmol) in ethanol (100
20 mL). The reaction was stirred at 0 °C for 45 and quenched with acetic acid (7.7 mL, 135 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h, then concentrated. The residue was diluted with 10% NH_4OH (aq) and extracted with EtOAc, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 50% EtOAc in Hexanes) to give **124**
25 (7.28 g, 56%) as a light yellow solid. m/z 195 $[\text{M}+\text{H}]^+$.

Compound 125: A solution of **124** (6.1 g, 31 mmol) in THF (25 mL) was added to a -78 °C solution of lithium (2 equiv.) in liq. NH_3 (10 mL). The reaction was stirred at -78 °C for 45 min, quenched with NH_4Cl (10 g), and warmed to room temperature. The mixture was diluted with water, extracted with EtOAc, and
30 concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **125** (1.7 g, 28%) as an oil. m/z 197 $[\text{M}+\text{H}]^+$.

Compound 126: A mixture of compound **125** (1.7 g, 8.7 mmol), ethylene glycol, and *p*-toluenesulfonic acid hydrate in benzene was heated to reflux for 4 h with azeotropic removal of water. The reaction mixture was cooled to room

temperature, washed with water, and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **126** (1.3 g, 62%) as an oil. m/z 241 $[M+H]^+$.

Compound 127: Compound **126** (1.3 g, 6.2 mmol) was taken up in CH_2Cl_2 (100 mL), then $MgSO_4$ (150 mg) and PDC (2 equiv.) were added. The reaction was stirred at room temperature for 2 d. The reaction mixture was filtered through a pad of silica (eluted with CH_2Cl_2) and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **127** (1.18 g, 92%) as a white solid. m/z 239 $[M+H]^+$.

Compound 128: Compound **127** (0.67 g, 2.8 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched KH_2PO_4 (aq) and extracted with EtOAc, then washed with water, dried with $MgSO_4$ and concentrated to give compound **128** (0.75 g, quantitative) as a solid. m/z 267 $[M+H]^+$.

Compound 129: A mixture of compound **128** (0.75 g, 2.8 mmol) and methyl hydrazine (1.6 equiv.) in ethanol was heated to 60 °C for 2 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, EtOAc) to give **129** (613 mg, 79%) as a solid. m/z 277 $[M+H]^+$.

Compound 130: Compound **129** (0.61 g, 2.2 mmol) was taken up in CH_2Cl_2 and 1,3-dibromo-5,5-dimethylhydantoin (0.55 equiv.) was added. The reaction was stirred at room temperature for 3 h. The reaction mixture was washed with 1 N Na_2CO_3 and concentrated. The crude residue was purified by column chromatography (silica gel, 10 to 30 % EtOAc in Hexanes) to give **130** (580 mg, 74%) as a solid. m/z 355, 357 (1:1) $[M+H]^+$.

Compound 131: A mixture of Compound **130** (0.58 g, 1.6 mmol), phenylboronic acid (1.25 equiv.), Ph_3P (0.3 equiv.), K_3PO_4 (3 equiv.) and DME was sparged with N_2 for 10 min. $Pd(OAc)_2$ (0.15 equiv.) was added and sparging with N_2 was continued for 10 min. The reaction was heated to 85 °C for 16 h. The reaction mixture was filtered and concentrated. The crude residue was purified by column chromatography (silica gel, 10 to 30 % EtOAc in Hexanes) to give compound **131** (360 mg, 63%) as an off-white solid. m/z 353 $[M+H]^+$.

Compound 132: Compound **131** (0.33 g, 0.94 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room

temperature. The reaction mixture was then concentrated. The reaction mixture was diluted with saturated NaHCO_3 and extracted with EtOAc (2×25 mL), then dried with MgSO_4 and concentrated to give compound **132** (300 mg, quantitative) as a solid. m/z 309 $[\text{M}+\text{H}]^+$.

5 **Compound 133:** Compound **132** (0.30 g, 0.94 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched KH_2PO_4 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 and concentrated to give compound **133** (300 mg, 95%) as a solid. m/z 337
10 $[\text{M}+\text{H}]^+$.

Compound 134: A mixture of hydroxylamine hydrochloride and **133** (0.30 g, 0.89 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and
15 concentrated to give compound **134** (300 mg, quantitative) as a solid. m/z 334 $[\text{M}+\text{H}]^+$.

Compound 135: Compound **134** (0.30 g, 0.89 mmol) was dissolved in a 1/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was
20 concentrated and quenched by addition of saturated KH_2PO_4 . The mixture was extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated to give compound **135** (300 mg, quantitative) as a solid. m/z 334 $[\text{M}+\text{H}]^+$.

Compound TX63541: Compound **135** (0.30 g, 0.89 mmol) was dissolved in
25 dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated.
30 The crude residue was purified by column chromatography (silica gel, 15 to 35 % EtOAc in Hexanes) to give compound **TX63541** (97 mg, 33%) as a solid. ^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1H), 7.51 (m, 2H), 7.45 (tt, 1H, $J = 2.1, 7.3$ Hz), 7.35 (m, 2H), 3.83 (s, 3H), 2.61 (m, 3H), 2.15 (dt, 1H, $J = 2.1, 12.7$ Hz), 2.04 (m, 1H), 1.75 (qd, 1H, $J = 6.6, 12.7$ Hz), 1.50 (s, 3H), 1.33 (s, 3H); m/z 332 $[\text{M}+\text{H}]^+$.

Compounds TX63791 and TX63792: The enantiomers of compound **TX63541** (488.9 mg) were separated using chiral HPLC (CHIRALPAK IA, 5 μ , 30x250 mm, 2:50:50 EtOH/EtOAc/Hexane) to afford two well resolved peaks. One is at 3.98 min, which gave **TX63791** (206.2 mg, 99.6% ee). ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 7.48 (m, 2H), 7.42 (m, 1H), 7.32 (m, 2H), 3.80 (s, 3H), 2.59 (m, 3H), 2.12 (t, 1H, *J* = 12.6 Hz), 2.01 (m, 1H), 1.73 (m, 1H), 1.47 (s, 3H), 1.30 (d, 3H, *J* = 6.0 Hz). And another one is at 5.04 min, which gave **TX63792** (220.7 mg, 99.8% ee). ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 7.48 (m, 2H), 7.42 (m, 1H), 7.32 (m, 2H), 3.80 (s, 3H), 2.59 (m, 3H), 2.12 (t, 1H, *J* = 12.6 Hz), 2.01 (m, 1H), 1.73 (m, 1H), 1.47 (s, 3H), 1.30 (d, 3H, *J* = 6.0 Hz).

Compound 136a-b: Compound **48** (0.360 g, 1.02 mmol) was taken up in DCM (30 mL) at room temperature. *N,N'*-Dibromodimethylhydantoin (0.169 g, 0.59 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to dryness and the residue chromatographed on silica gel (230–400 mesh, 24 g) using 10% EtOAc/Hexanes to give **136b** (0.1057 g), *m/z* 433.0, [M+H]⁺; and **136a** (0.1141 g). *m/z* 389.0, [M+H]⁺.

Compound 137: The mixture of **136a** (105.7 mg) and **136b** (114.1 mg) was taken up in DME. PhB(OH)₂ (1.5 eq), Ph₃P (0.2 eq.) and K₃PO₄ (3.0 eq.) were added, and the mixture was bubbled with N₂ for 10 min. Pd(OAc)₂ (0.1 eq) was added and the mixture was bubbled with N₂ for 10 min. Then the mixture was stirred at 85 °C for 9 h. The reaction mixture was filtered, concentrated. The crude residue was purified by column chromatography to give corresponding cross coupled products as a mixture (**a**: 81.6 mg, **b**: 37.4 mg), which was taken up in MeOH and HCl (aq, 3N) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted with EtOAc and washed with saturated NaHCO₃ (aq), then dried with MgSO₄ and concentrated to give **137** (108.9 mg). *m/z* [M+H]⁺ 385.1.

Compound 138: Compound **137** (0.116 g, 0.30 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH₂PO₄ (aq), extracted with EtOAc (2 $\times$ 25 mL) and washed with brine, then dried with MgSO₄ and concentrated to give compound **138** (134.2 mg, 100%). *m/z* [M+H]⁺ 413.1.

Compound 139: A mixture of hydroxylamine hydrochloride and **117** (0.134 g, 0.33 mmol) in EtOH was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with EtOAc, then dried with MgSO₄ and concentrated to give compound **139** (124.9 mg, 94%), m/z [M+H]⁺ 410.2.

Compound 140: Compound **139** (0.1249 g, 0.31 mmol) was dissolved in a 1/1 MeOH/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH₂PO₄. The mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated to give compound **140** (119.5 mg, 94%), m/z [M+H]⁺ 410.2.

Compound TX63544: Compound **140** (0.1195 g, 0.29 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 5–30 % EtOAc/Hexanes) to give compound **TX63544** (60.9 mg, 52%). ¹H NMR (500 MHz, CDCl₃) δ 8.60 (s, 1H), 7.31–7.28 (m, 5H), 7.26–7.21 (m, 3H), 7.15–7.13 (m, 2H), 2.80 (dd, 1H, J = 5.1, 16.4 Hz), 2.67–2.60 (m, 1H), 2.28 (dd, 1H, J = 2.1, 11.6 Hz), 1.98–1.86 (m, 2H), 1.60 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H); m/z [M+H]⁺ 408.2.

Compound 141a: A mixture of Compound **68** (0.23 g, 0.62 mmol), isopropenyl pinacol boronate (1.25 equiv.), Ph₃P (0.3 equiv.), K₃PO₄ (3 equiv.) and DME was sparged with N₂ for 10 min. Pd(OAc)₂ (0.15 equiv.) was added and sparging with N₂ was continued for 10 min. The reaction was heated to 85 °C for 16 h. The reaction mixture was filtered and concentrated. The crude residue was purified by column chromatography (silica gel, 10 to 30 % EtOAc in Hexanes) to give compound **141a** (85 mg, 41%) as a solid. m/z 331 [M+H]⁺.

Compound 142a: Compound **141a** (85 mg, 0.26 mmol) was taken up in THF under N₂ and 10% Pd/C added. The flask was rigorously purged with H₂ and stirred for 2 d at room temperature. The reaction mixture was filtered and concentrated to give compound **142a** (85 mg, 99%) as a solid. m/z 333 [M+H]⁺.

Compound 143a: Compound **142a** (85 mg, 0.26 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The reaction mixture was diluted with saturated NaHCO₃ and extracted with EtOAc (2 × 25 mL), then dried with MgSO₄ and concentrated to give compound **143a** (70 mg, 95%) as a solid. m/z 289 [M+H]⁺.

Compound 144a: Compound **143a** (70 mg, 0.24 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched KH₂PO₄ (aq) and extracted with EtOAc, then washed with brine, dried with MgSO₄ and concentrated to give compound **144a** (80 mg, quantitative) as a solid. m/z 317 [M+H]⁺.

Compound 145a: A mixture of hydroxylamine hydrochloride and **144a** (80 mg, 0.24 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated to give compound **145a** (80 mg, quantitative) as a solid. m/z 314 [M+H]⁺.

Compound 146a: Compound **145a** (80 mg, 0.24 mmol) was dissolved in a 1/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH₂PO₄. The mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated to give compound **146a** (75 mg, 99%) as a solid. m/z 314 [M+H]⁺.

Compound TX63547: Compound **146a** (75 mg, 0.24 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 15 to 35 % EtOAc in Hexanes) to give compound **TX63547** (11 mg, 15%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ 8.50 (s, 1H), 3.80 (s, 3H), 3.05 (septet, 1H, J = 7.0 Hz), 2.84 (ddd, 1H, J = 7.0, 11.7, 15.7 Hz), 2.58 (ddd, 1H, J = 7.0, 11.7, 15.7 Hz), 2.16 (dd,

1H, $J = 2.1, 11.9$ Hz), 1.88 (m, 2H), 1.50 (s, 3H), 1.32 (d, 3H, $J = 7.1$ Hz), 1.29 (s, 3H), 1.29 (d, 3H, $J = 7.1$ Hz), 1.24 (s, 3H); m/z 312 $[M+H]^+$.

Compound 141b: Compound **68** (0.371 g, 1.00 mmol), K_2CO_3 (0.417 g, 3.02 mmol), 1-cyclohexenylboronic acid pinacol ester (0.269 g, 0.23 mmol) and dioxane (15 mL) were mixed and the reaction was sparged with N_2 for 2-3 minutes. Pd(dppf) Cl_2 (0.079 g, 0.097 mmol) was added and the reaction was sparged with N_2 for about 5 minutes. The vial was tightly sealed and heated at 100 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ solution (30 mL), the layers were separated, and the organic layer dried over $MgSO_4$, filtered and concentrated to an oil. The oil was chromatographed on silica gel (230–400 mesh, 19 g) using 20% EtOAc/Hexane to give **141b** (151 mg, 40%) as a glass/white solid. m/z $[M+H]^+$ 371.2.

Compound 142b: Compound **141b** (0.147 g, 0.40 mmol) was taken up in EtOH (20 mL), and the flask was flushed with nitrogen gas. 10% Pd/C (0.035 g) was added and the flask was evacuated and flushed with H_2 three times and was stirred overnight plus 6 hours under a balloon of H_2 at room temperature. The catalyst was filtered off and the filtrate concentrated give **142b** (139 mg, 93%) as a clear foam/glass, m/z $[M+H]^+$ 373.1.

Compound 143b: Compound **142b** (0.139 g, 0.37 mmol) was treated according to the procedure for **37a** to give **143b** (110.6 mg, 92%) as a glass/solid. m/z $[M+H]^+$ 329.1.

Compound 144b: Compound **143b** (0.1106 g, 0.34 mmol) was treated according to the procedure for **143a** to give **144a** (128 mg, quantitative). m/z $[M+H]^+$ 357.1.

Compound 145b: Compound **144b** (0.128 g, 0.36 mmol) was treated according to the procedure for **144a** to give **145a** (111.4 mg, 89%) as a foam. m/z $[M+H]^+$ 354.1.

Compound 146b: Compound **145b** (0.1114 g, 0.32 mmol) was treated according to the procedure for **145a** to give **146a** (111.7 mg, 97%) as an off-white foam. m/z $[M+H]^+$ 354.0.

Compound TX63591: Compound **146b** (0.111 g, 0.31 mmol) was treated according to the procedure for **146a** to give **TX63547** and chromatographed on silica gel (230–400 mesh, 12 g) using 3:1 Hexanes/EtOAc and was chromatographed a

second time on silica gel (230–400 mesh, 8 g) using 5% methyl *tert*-butylether in DCM to give **TX63591** (14 mg, 12%). ¹H NMR (500 MHz, CDCl₃) δ 8.45 (s, 1H), 3.75 (s, 3H), 2.82 (dd, 1H, J = 15, 5 Hz), 2.51–2.62 (m, 2H), 2.12 (dd, 1H, J=10, 2.5 Hz), 1.74–1.89 (m, 7H), 1.50–1.58 (m, 3H), 1.46 (s, 3H), 1.29–1.37 (m, 2H), 1.25 (s, 3H), 1.23 (s, 3H).

Compound 147: Compound **68** (0.151 g, 0.41 mmol), K₂CO₃ (0.176 g, 1.29 mmol), benzylboronic acid pinacol ester (0.176 g, 0.8 mmol), Pd(dppf)Cl₂ (0.038 g, 0.0046 mmol) and dioxane (8 mL) were reacted under nitrogen at 90 °C for 1.5 hours and then overnight at 100 °C. More Pd(dppf)Cl₂ (0.041 g, 0.005 mmol) was added and the reaction mixture was heated at 120 °C overnight and purified by chromatography on silica gel (230–400 mesh, 9.9 g) eluting with 5:1 Hexanes/EtOAc, then 3:1 Hexanes/EtOAc to give **147** as a mixture with dehalogenated starting bromopyrazole as an oil, (0.0736 g), *m/z* [M+H]⁺ 381.1.

Compound 148: Compound **147** (73.6 mg, 0.19 mmol) was taken up in MeOH, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The reaction mixture was extracted with EtOAc (2 × 25 mL) and washed saturated NaHCO₃, then dried with MgSO₄ and concentrated to give compound **148** (58.8 mg) as a solid. *m/z* 337.1 [M+H]⁺.

Compound 149: Compound **148** (58.8 mg, 0.18 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH₂PO₄ (aq), extracted with EtOAc (2 × 25 mL) and washed with brine, then dried with MgSO₄ and concentrated to give compound **149** (74 mg) as a solid This was used directly in the next step.

Compound 150: A mixture of hydroxylamine hydrochloride and **149** (74 mg, 0.2 mmol) in EtOH was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with EtOAc, then dried with MgSO₄ and concentrated to give compound **150** (71 mg) as a solid. *m/z* 362.1 [M+H]⁺.

Compound 151: Compound **150** (71 mg, 0.2 mmol) was dissolved in a 1/1 MeOH/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH₂PO₄. The mixture was

extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated. The residue was chromatographed on silica gel (230–400 mesh, 11 g) using 50% Hexanes/EtOAc to give **151** (23 mg) as a solid. m/z $[\text{M}+\text{H}]^+$ 362.1.

Compound TX63550: Compound **151** (23 mg, 0.063 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. Br_2 was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (230–400 mesh, 7g) using 50% Hexanes/EtOAc to give **TX63550** (8.3 mg). ^1H NMR (500 MHz, CDCl_3) δ 8.45 (s, 1H), 7.28 (dd, 2H, $J = 7.3, 7.5$ Hz), 7.21 (t, 1H, $J = 7.3$ Hz), 7.04 (d, 2H, $J = 7.4$ Hz), 3.90 (s, 2H), 3.65 (s, 3H), 2.57 (dd, 1H, $J = 5.9, 15.8$ Hz), 2.35 (m, 1H), 2.14 (dd, 1H, $J = 1.9, 11.8$ Hz), 1.90–1.77 (m, 2H), 1.47 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H); m/z $[\text{M}+\text{H}]^+$ 360.1.

Compound 152: Compound **130** (355 mg, 1.28 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The reaction mixture was diluted with saturated NaHCO_3 and extracted with EtOAc (2×25 mL), then dried with MgSO_4 and concentrated to give compound **152** (305 mg, quantitative) as a solid. m/z 233 $[\text{M}+\text{H}]^+$.

Compound 153: Compound **152** (305 mg, 1.28 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched KH_2PO_4 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 and concentrated to give compound **153** (330 mg, 99%) as a solid. m/z 261 $[\text{M}+\text{H}]^+$.

Compound 154: A mixture of hydroxylamine hydrochloride and **153** (330 mg, 1.27 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **154** (320 mg, 98%) as a solid. m/z 258 $[\text{M}+\text{H}]^+$.

Compound 155: Compound **154** (320 mg, 1.24 mmol) was dissolved in a 1/1 methanol/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was

concentrated and quenched by addition of saturated KH_2PO_4 . The mixture was extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated to give compound **155** (320 mg, quantitative) as a solid. m/z 258 $[\text{M}+\text{H}]^+$.

5 **Compound TX63551:** Compound **155** (320 mg, 1.24 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction
10 mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 15 to 35 % EtOAc in Hexanes) to give compound **TX63551** (120 mg, 38%) as a solid. ^1H NMR (500 MHz, CDCl_3) δ 8.46 (s, 1H), 7.08 (s, 1H), 3.87 (s, 3H), 2.75 (dd, 1H, $J = 6.3$, 16.0 Hz), 2.57 (m, 2H), 2.09 (dt, 1H, $J = 1.8$, 12.4 Hz), 2.02 (dd, 1H, $J = 7.1$, 13.7
15 Hz), 1.74 (m, 1H), 1.44 (s, 3H), 1.31 (d, 3H, $J = 6.7$ Hz); m/z 256 $[\text{M}+\text{H}]^+$.

Compound 156: A solution of compound **1** (2.50 g, 19.8 mmol) and acrylamide (2.15 g, 30.2 mmol) in Et_3N (50 mL) was heated at 85 °C for 16 h. The reaction mixture was cooled to room temperature and the brown solid isolated by filtration. The crude solid was triturated with EtOAc to give **156** (3.77 g, 96%) as a
20 light brown solid. m/z 198 $[\text{M}+\text{H}]^+$.

Compound 157: Compound **156** (3.75 g, 19.0 mmol) was taken up in HOAc (37.5 mL), divided into 3 equal portions and sealed in microwave vials. Each vial was heated to 160 °C for 1 h in the microwave. The reaction mixtures were combined, diluted with EtOH (20 mL), and heated to reflux for 20 min, then cooled to
25 room temperature. The mixture was filtered and the filtrate washed with EtOAc to give **157** (2.48 g, 73%) as a light brown solid. m/z 180 $[\text{M}+\text{H}]^+$.

Compound 158: NaH (1.0 equiv.) was added to a 0 °C solution of **157** (1.5 g, 8.4 mmol) in DMF/THF (2.3/1, 30 mL) and the mixture stirred for 45 min. MeI (1.5 equiv.) was added and the reaction warmed to room temperature. After 1.5 h at room
30 temperature the reaction was quenched with saturated NH_4Cl and extracted with CH_2Cl_2 , then washed with water, dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 100 % EtOAc in Hexanes) to give **158** (1.1 g, 68%) as a light yellow solid. m/z 194 $[\text{M}+\text{H}]^+$.

Compound 159: Compound **158** (600 mg, 3.1 mmol) was taken up in AcOH/water (19/1, 12 mL) under N₂ and PtO₂ (120 mg) added. The flask was rigorously purged with H₂ and stirred for 16 h at room temperature. The reaction mixture was filtered through Celite, eluted with EtOAc, and concentrated. The crude residue was taken up in CH₂Cl₂, dried with MgSO₄, and concentrated to give compound **159** (864 mg, quantitative) as a viscous oil. m/z 198 [M+H]⁺.

Compound 160: TPAP (107 mg, 0.30 mmol) was added to a room temperature mixture of compound **159** (864 mg, 3.1 mmol), NMO (770 mg, 6.6 mmol), and 4 Å molecular sieves (2 g) in CH₂Cl₂ (40 mL). The reaction mixture was stirred at room temperature for 1 h. The mixture was filtered through a pad of silica, eluted with acetone/CH₂Cl₂ (1/1, 100 mL) and concentrated. The residue was taken up in CH₂Cl₂, washed with 1 N HCl (aq) and water, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 50 % Acetone in Hexanes) to give **160** (480 mg, 79%) as a white solid. m/z 196 [M+H]⁺.

Compound 161: Compound **160** (120 mg, 0.61 mmol) was taken up in ethyl formate, cooled to 0 °C, and 25% sodium methoxide (25 wt% solution in MeOH) was added. The mixture was stirred for 1 h at 0 °C, then warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with 12 N HCl (0.55 mL) and extracted with CH₂Cl₂, then dried with MgSO₄ and concentrated to give crude compound **161**: m/z 224 [M+H]⁺.

Compound 162: A mixture of crude compound **161** and methyl hydrazine (52 mL, 0.98 mmol) in ethanol (6.1 mL) was heated to 60 °C for 3 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 10 % MeOH in CH₂Cl₂) to give **162** (134 mg, 93%) as an oil. m/z 234 [M+H]⁺.

Compound 163: A solution of 1,3-dibromo-5,5-dimethylhydantoin (107 mg, 0.37 mmol) in CH₂Cl₂ (3 mL) was added to a room temperature solution of compound **162** (134 mg, 0.57 mmol) in CH₂Cl₂ (3 mL). The reaction was stirred for 5 h at room temperature. The reaction mixture was directly purified by successive column chromatography, first directly loaded (silica gel, 0 to 70 % Acetone in Hexanes), then (silica gel, 0 to 5 % MeOH in CH₂Cl₂) to give **163** (87 mg, 49%) as an oil. m/z 312, 314 (1:1), [M+H]⁺.

Compound 164: A mixture of Compound **163** (87 mg, 0.28 mmol), 3-phenylboronic acid (1.5 equiv.), Ph_3P (0.2 equiv.), K_3PO_4 (3.0 equiv.) and DME was sparged with N_2 for 10 min. $\text{Pd}(\text{OAc})_2$ (0.1 equiv.) was added and sparging with N_2 was continued for 10 min. The reaction vial was sealed and heated to 110 °C for 2.5 h in the microwave. The reaction mixture was filtered and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 65 % Acetone in Hexanes) to give compound **164** (82 mg, 95%) as a white solid. m/z 310 $[\text{M}+\text{H}]^+$.

Compound 165: A solution of LDA (2.0 equiv.) in THF was added to a -78 °C solution of **164** (40 mg, 0.13 mmol) in THF (1.3 mL). The reaction was stirred at -78 °C for 30 min, then a solution of PhSeCl (3 equiv.) in THF (0.4 mL) was added. The reaction was stirred at -78 °C for an additional 1 h, then quenched with saturated NH_4Cl (aq) and warmed to room temperature. The reaction mixture was extracted with EtOAc, then washed with water, dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 100 % EtOAc in Hexanes) to give compound **165** (27 mg, 45%) as a yellow solid. m/z 466 $[\text{M}+\text{H}]^+$.

Compound 166: Compound **165** (27 mg, 0.058 mmol) was taken up in EtOAc/THF (3/1, 1.2 mL), and H_2O_2 (30%, 5 equiv.) was added. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted EtOAc, washed with saturated Na_2SO_3 (aq) and water, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 100 % EtOAc in Hexanes) to give compound **166** (16 mg, 90%) as a white solid. m/z 308 $[\text{M}+\text{H}]^+$.

Compound 167: Iodine (2 equiv.) was added to a room temperature solution of compound **166** (14.2 mg, 0.046 mmol) in pyridine/ CCl_4 (1/2, 0.69 mL). The reaction mixture was stirred for 5 h at room temperature, then for 16 h at 50 °C, and finally for 20 h at 65 °C. The reaction was cooled to room temperature and diluted with EtOAc. The mixture was washed with saturated Na_2SO_3 (aq), water, and brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 100 % EtOAc in Hexanes) to give compound **167** (12 mg, 60%) as a yellow solid. m/z 434 $[\text{M}+\text{H}]^+$.

Compound TX63568: Compound **167** (11 mg, 0.036 mmol), $\text{Zn}(\text{CN})_2$ (3 equiv.) and $\text{Pd}(\text{PPh}_3)_4$ (0.2 equiv.) were taken up in degassed DMF (0.5 mL). The vial was purged with N_2 , sealed and the reaction stirred for 20 min at 80 °C. The reaction mixture was diluted with EtOAc and washed with water, then dried with

MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 0 to 50 % EtOAc in Hexanes) to give compound **TX63568** (7.5 mg, 89%) as a light yellow solid. NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.49 (t, 2H, J = 7.0 Hz), 7.43 (t, 1H, J = 7.2 Hz), 7.32 (d, 2H, J = 6.9 Hz), 3.88 (dd, 1H, J = 2.8, 13.2 Hz), 3.80 (s, 3H), 3.12 (s, 3H), 2.72 (ddd, 1H, J = 1.3, 6.6, 16.4 Hz), 2.63 (ddd, 1H, J = 6.6, 11.4, 16.3 Hz), 2.30 (m, 1H), 2.00 (m, 1H), 1.35 (s, 3H); m/z 333 [M+H]⁺.

Compound 169: Compound **25** (0.294 g, 1.17 mmol) was taken up in DCM (50 mL). MgBr-Et₂O (0.777 g, 3.0 mmol) and *i*Pr₂EtN (0.4 mL, 2.3 mmol) were added sequentially and the reaction mixture was stirred at room temperature for about 15 minutes, gradually turning orange. Benzoyl chloride (0.342 g, 2.43 mmol) in DCM (2 mL) was added dropwise and the mixture was stirred overnight at room temperature. The reaction was quenched by adding saturated aqueous NaHCO₃ solution, the layers were separated, and the organic layer was dried over MgSO₄, filtered and concentrated to an oil to afford crude **168**. The residue was taken up in EtOH (25 mL) and treated with hydrazine monohydrate (0.63 g, 12.6 mmol) in EtOH and the mixture was heated at 63 °C for about 1 hour and was then concentrated to a yellow oil. The oil was chromatographed on silica gel (230–400 mesh, 15 g) using 50% EtOAc/Hexane to yield **169** (158 mg, 38%) as an almost clear oil. m/z [M+H]⁺ 353.1.

Compound 170: Compound **169** (0.158 g, 0.45 mmol) was taken up in MeOH, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted with EtOAc and washed with saturated NaHCO₃ (aq), then dried with MgSO₄ and concentrated to give compound **170** (174 mg, quantitative) as an oil. m/z [M+H]⁺ 309.0.

Compound 171: Compound **170** (0.169 g, 0.55 mmol) was taken up in ethyl formate, and sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with EtOAc and washed with KH₂PO₄ (aq), then dried with MgSO₄ and concentrated to give compound **171** (154.8 mg, 84%). m/z [M+H]⁺ 337.0.

Compound 172: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **171** (0.1548 g, 0.46 mmol). A 9:1 mixture of EtOH/water was added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in

EtOAc, then dried with MgSO_4 and concentrated to give compound **172** (128 mg, 83%) as a light yellow solid. m/z $[\text{M}+\text{H}]^+$ 334.0.

Compound 173: Compound **172** (0.128 g, 0.38 mmol) was dissolved in a 3:1 MeOH/THF mixture, and sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 , and the reaction mixture was concentrated. The residue was extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 50% EtOAc/Hexanes) to give compound **173** (129 mg, quantitative) as a yellow glass/solid. m/z $[\text{M}+\text{H}]^+$ 334.0.

Compound TX63579: A mixture of compound **173** (0.129 g, 0.39 mmol) and DDQ (1.3 eq) were taken up in benzene. The mixture was stirred at reflux for 4.5 h. After cooling to room temperature, the reaction mixture was concentrated. The crude residue was chromatographed on silica gel (230–400 mesh, 11 g) using 3:1 Hexanes/EtOAc to give **TX63579** (35.47 mg, 27%). ^1H NMR (500 MHz, d_6 -DMSO) δ 13.05 (s, 1H), 8.55 (s, 1H), 7.61 (d, 2H), 7.47 (dd, 2H, $J = 7.4, 7.5$ Hz), 7.35 (t, 1H, $J = 7.4$ Hz), 2.87 (dd, 1H, $J = 5.5, 15.8$ Hz), 2.76–2.69 (m, 1H), 2.26 (d, 1H), 1.98–1.86 (m, 2H), 1.45 (s, 3H), 1.24 (s, 3H), 1.15 (s, 3H); m/z $[\text{M}+\text{H}]^+$ 332.0.

Compound 174: A solution of acetamide hydrochloride (0.68 g, 7.2 mmol) and piperidine (0.60 g, 7.0 mmol) in *i*-PrOH (10 mL) was stirred at room temperature for 15 min, then compound **26** (0.20 g, 0.71 mmol) was added. The reaction mixture was heated at reflux for 3 d, then concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 25 % EtOAc in Hexanes) to give **174** (0.12 g, 56%) as a solid. m/z 303 $[\text{M}+\text{H}]^+$.

Compound 175a: *O*-Methylisourea hemisulfate (0.946g, 7.7 mmol) and piperidine (0.58 g, 6.8 mmol) were taken up in *i*PrOH (15 mL), and the mixture was stirred at room temperature for approximately 15 min. Compound **174** (0.212 g, 0.76 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min and then heated to reflux for 4 d. The *i*PrOH was replaced with *n*-BuOH and more *O*-methylisourea hemisulfate (0.432 g, 3.5 mmol) was added. The reaction mixture was heated to reflux overnight. After cooling to room temperature, the reaction mixture was concentrated. The residue was extracted with EtOAc (80 mL) and washed with saturated aq. NaHCO_3 (15 mL), and brine (15 mL), then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography

(silica gel, 20% EtOAc/Hexanes) to give a mixture of three components (364 mg): m/z 319.2 $[M+H]^+$.

Table 8: Compounds 175b-175o (Scheme 31).

Compound Name	R	9 (mmol)	Amidine (mmol)	Piperidine (mmol)	Yield (%)
175b	Me	0.71	7.2	7.0	56
175c	<i>i</i> -Pr	1.091	10.93	6.60	63
175d	H	1.081	10.85	6.46	75
175e	Ph	1.091	11.24	6.77	75
175f	<i>t</i> -Bu	1.07	7.3	5.35	52
175g	CF ₃	1.07	10.7	5.35	88
175h	4-Cl-Ph	1.242	5.23	3.13	40
175i	2-Cl-Ph	1.25	5.58	3.23	Quant.
175j	3-Me-Ph	1.118	5.86	3.53	39
175k	4-MeO-Ph	1.258	5.4	3.23	32
175l	Me-thiazole	1.19	5.75	3.43	Quant.
175m	3-pyridyl	1.079	6.34	3.84	44
175n	4-pyridyl	1.28	12.82	7.68	Quant.
175o	2-pyridyl	1.09	6.34	3.84	95

General method F: Compound **174** (See Table 8 for the amount), substituted
 5 amidine (See Table 8 for the amount) and piperidine (See Table 8 for the amount) were taken up in *i*-PrOH (10 mL), and the mixture was stirred at 85 °C for 48 h in a sealed tube. After cooling to room temperature, the reaction mixture was concentrated. The residue was extracted with CHCl₃ and washed with NH₄Cl (aq, 10%), brine, then dried with MgSO₄ and concentrated. The crude residue was
 10 purified by column chromatography (silica gel, EtOAc/Hexanes or MeOH/CHCl₃) to give the corresponding derivatives:

Compound 175b: 0.12 g, 56%: m/z 303 $[M+H]^+$.

Compound 175c: 0.2282 g, 63%: m/z 331 $[M+H]^+$.

Compound 175d: 0.233 g, 75%: m/z 289 $[M+H]^+$.

15 **Compound 175e:** 0.307 g, 75%: m/z 365 $[M+H]^+$.

Compound 175f: 0.190 g, 52%: m/z 345 $[M+H]^+$.

Compound 175g: 0.337 g, 88%: m/z 357 $[M+H]^+$.

Compound 175h: 0.2 g, 40%: m/z 399, 401 (3:1) $[M+H]^+$.

Compound 175i: 1.38 g, >100%: m/z 399/401 (39/14%) $[M+H]^+$, 155/157 (100/36%).

Compound 175j: 0.164 g, 39%: m/z 379 $[M+H]^+$.

5 **Compound 175k:** 0.161 g, 32%: m/z 395 $[M+H]^+$.

Compound 175l: 0.92 g, >100%: m/z 386 (93%) $[M+H]^+$, 143 (64%) and 126 (100%).

Compound 175m: 0.172 g, 44%: m/z 366 $[M+H]^+$.

Compound 175n: 1.05 g, >100%: m/z 366 (83%) $[M+H]^+$ and 190 (100%).

10 **Compound 175o:** 0.38 g, 95%: m/z 366 (100%) $[M+H]^+$.

Compound 176a: Compound **175a** (0.364 g) was taken up in MeOH, and HCl (aq, 1 N) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted with EtOAc and washed with saturated NaHCO_3 (aq), then dried with MgSO_4 and concentrated to give
15 a mixture (0.336 g): m/z 275 $[M+H]^+$.

Table 9: Compounds 176b-176o (Scheme 31).

Compound Name	R	175b-o (mmol)	3N HCl (mL)	Solvent	Yield (%)
176b	Me	0.50	Not given	MeOH	quantitative
176c	<i>i</i> -Pr	0.69	2	MeOH (10 mL)	89
176d	H	0.809	2	MeOH (10 mL)	93
176e	Ph	0.844	2	MeOH:THF (1:1) (20 mL)	quantitative
176f	<i>t</i> -Bu	0.552	2	MeOH (10 mL)	84
176g	CF_3	0.944	2	MeOH (10 mL)	65
176h	4-Cl-Ph	0.502	4	MeOH:THF (1:1) (20 mL)	87
176i	2-Cl-Ph	1.25	5	MeOH (25 mL)	73
176j	3-Me-Ph	0.433	4	MeOH:THF (1:1) (20 mL)	96
176k	4-MeO-Ph	0.409	4	MeOH:THF (1:1) (20 mL)	88
176l	Me-thiazole	1.19	5 mL (6N)	MeOH (20 mL)	92

Compound Name	R	175b-o (mmol)	3N HCl (mL)	Solvent	Yield (%)
176m	3-pyridyl	0.471	4	MeOH:THF (1:1) (20 mL)	quantitative
176n	4-pyridyl	1.28	5 mL (6N)	MeOH (25 mL)	66
176o	2-pyridyl	1.06	5 mL (6 N)	MeOH (20 mL)	72

General method G: Compound **175b-o** (see Table 9 for the amount) was taken up in solvent (see Table 9 for the amount), and HCl (aq) (see Table 9 for the amount) was added. The mixture was stirred under N₂ at room temperature for 16 h. The reaction mixture was then concentrated. The residue was basified with NH₄OH (aq., 10%) to pH~9–10, extracted with CHCl₃ and washed with saturated NaCl (aq), then dried with MgSO₄ and concentrated to give the corresponding derivatives:

Compound 176b: 0.14 g, quantitative: m/z 259 [M+H]⁺.

Compound 176c: 0.176 g, 89%: m/z 287 [M+H]⁺.

Compound 176d: 0.184 g, 93%: m/z 245 [M+H]⁺.

10 **Compound 176e:** 0.287 g, quantitative: m/z 321 [M+H]⁺.

Compound 176f: 0.139 g, 84%: m/z 301 [M+H]⁺.

Compound 176g: 0.191 g, 65%: m/z 313 [M+H]⁺.

Compound 176h: 0.155 g, 87%: m/z 355, 357 (3:1) [M+H]⁺.

Compound 176i: 0.32 g, 73%: m/z 355/357 (100/74%) [M+H]⁺.

15 **Compound 176j:** 0.139 g, 96%: m/z 335 [M+H]⁺.

Compound 176k: 0.127 g, 88%: m/z 351 [M+H]⁺.

Compound 176l: 0.37 g, 92%: m/z 342 (100%), [M+H]⁺.

Compound 176m: 0.174 g, 100%: m/z 322 [M+H]⁺.

Compound 176n: 0.27 g, 66%: m/z 322 (100%), [M+H]⁺.

20 **Compound 176o:** 0.24 g, 72%: m/z 322 (100%), [M+H]⁺.

Compound 177a: Compound **176a** (0.336 g, 1.2 mmol) was taken up in ethyl formate (20 mL), and 30% NaOMe in MeOH (1.56 mL, 28.4 mmol) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with EtOAc and washed with KH_2PO_4 (aq), then dried with MgSO_4 and concentrated to give the compound **177a** (0.152 g, 66% over 3 steps): m/z 303 $[\text{M}+\text{H}]^+$.

Table 10: Compounds 177b-o (Scheme 31).

Compound Name	R	176b-o (mmol)	EtO_2CH (mL)	MeONa in MeOH (30% w/w, mL)	Benzene (mL)	Yield (%)
177b	Me	0.500	Not given	Not given	Not given	92
177c	<i>i</i> -Pr	0.616	0.50	0.60	20	quantitative
177d	H	0.752	0.61	0.71	20	95
177e	Ph	0.844	0.68	0.80	20	84
177f	<i>t</i> -Bu	0.464	0.37	0.44	10	quantitative
177g	CF_3	0.613	0.50	0.57	10	quantitative
177h	4-Cl-Ph	0.437	0.35	0.41	10	99
177i	2-Cl-Ph	0.910	0.73	0.85	20	91
177j	3-Me-Ph	0.417	0.34	0.39	10	89
177k	4-MeO-Ph	0.362	0.30	0.34	10	quantitative
177l	Me-thiazole	1.10	0.89	1.0	25	94
177m	3-pyridyl	0.471	0.38	0.44	10	83
177n	4-pyridyl	0.850	0.68	0.80	20	quantitative
177o	2-pyridyl	0.76	0.62	0.72	20	82

General method H: Compound **176b-o** (see Table 10 for the amount) and ethyl formate (see Table 10 for the amount) were taken up in benzene (see Table 10 for the amount), and 30% NaOMe in MeOH (see Table 10 for the amount) was added. The mixture was stirred under N_2 at room temperature for 16 h. The reaction mixture was then concentrated. The residue was extracted with EtOAc and washed with saturated KH_2PO_4 (aq), saturated NaCl (aq), then dried with MgSO_4 and concentrated to give the corresponding derivatives:

Compound 177b: 0.13 g, 92%: m/z 287 $[\text{M}+\text{H}]^+$.

- Compound 177c:** 0.206 g, quantitative: m/z 315 $[M+H]^+$.
- Compound 177d:** 0.194 g, 95%: m/z 273 $[M+H]^+$.
- Compound 177e:** 0.248 g, 84%: m/z 349 $[M+H]^+$.
- Compound 177f:** 0.162 g, quantitative: m/z 329 $[M+H]^+$.
- 5 **Compound 177g:** 0.228 g, quantitative: m/z 329 $[M+H]^+$.
- Compound 177h:** 0.166 g, 99%: m/z 397, 399 (3:1) $[M+H]^+$.
- Compound 177i:** 0.32 g, 91%: m/z 383/385 (100/42%), $[M+H]^+$.
- Compound 177j:** 0.134 g, 89%: m/z 363 $[M+H]^+$.
- Compound 177k:** 0.156 g, quantitative: m/z 379 $[M+H]^+$.
- 10 **Compound 177l:** 0.38 g, 94%: m/z 392 (13%) $[M+Na]^+$ and 370 (100%) $[M+H]^+$.
- Compound 177m:** 0.137 g, 83%: m/z 350 $[M+H]^+$.
- Compound 177n:** 0.35 g, >100%: m/z 350 (100%) $[M+H]^+$.
- Compound 177o:** 0.22 g, 82%: m/z 350 (100%) $[M+H]^+$.
- 15 **Compound 178a:** A solution of 0.1 N hydroxylamine hydrochloride (5.5 mL, 0.55 mmol) was added to compound **177a** (0.152 g, 0.5 mmol). A 9/1 mixture of ethanol/water was added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, then dried with $MgSO_4$ and concentrated. The crude
- 20 residue was purified by column chromatography (silica gel, 25% EtOAc/Hexanes) to give the compound **178a** (18 mg, 12%): m/z 300 $[M+H]^+$.

Table 11: Compound 178b-178o (Scheme 31).

Compound Name	R	177b-o (mmol)	$NH_2OH \cdot HCl$ (mmol)	Ethanol (mL)	Yield (%)
178b	Me	0.45	Not given	Not given	quantitative
178c	<i>i</i> -Pr	0.616	0.921	10	96
178d	H	0.712	1.065	10	88
178e	Ph	0.711	1.065	10	quantitative
178f	<i>t</i> -Bu	0.464	0.69	10	quantitative
178g	CF_3	0.613	0.92	10	85
178h	4-Cl-Ph	0.434	0.65	20	90
178i	2-Cl-Ph	0.82	1.24	20	quantitative
178j	3-Me-Ph	0.369	0.55	10	quantitative

Compound Name	R	177b-o (mmol)	NH ₂ OH·HCl (mmol)	Ethanol (mL)	Yield (%)
178k	4-MeO-Ph	0.362	0.55	10	quantitative
178l	Me-thiazole	1.02	1.58	20	quantitative
178m	3-pyridyl	0.391	0.59	10	82
178n	4-pyridyl	0.85	1.29	50	83
178o	2-pyridyl	0.63	0.94	25	45

General method I: Compound **177b-o** (see Table 11 for the amount) was taken up in EtOH (see Table 11 for the amount), and hydroxylamine hydrochloride (see Table 11 for the amount) was added. The mixture was stirred overnight at 50 °C under N₂. After cooling to room temperature, the reaction mixture was concentrated.

- 5 The residue was taken up in EtOAc and washed with saturated NaHCO₃ (aq), saturated NaCl (aq), then dried with MgSO₄ and concentrated to give the corresponding derivatives:

Compound 178b: 0.13 g, quantitative: *m/z* 284 [M+H]⁺.

Compound 178c: 0.183 g, 96%: *m/z* 312 [M+H]⁺.

10 **Compound 178d:** 0.168 g, 88%: *m/z* 270 [M+H]⁺.

Compound 178e: 0.247 g, quantitative: *m/z* 346 [M+H]⁺.

Compound 178f: 0.167 g, quantitative: *m/z* 326 [M+H]⁺.

Compound 178g: 0.175 g, 85%: *m/z* 338 [M+H]⁺.

Compound 178h: 0.149 g, 90%: *m/z* 380, 382 (3:1) [M+H]⁺.

15 **Compound 178i:** 0.31 g, ~100%: *m/z* 380/382 (100/63%) [M+H]⁺.

Compound 178j: 0.152 g, quantitative: *m/z* 360 [M+H]⁺.

Compound 178k: 0.146 g, quantitative: *m/z* 376 [M+H]⁺.

Compound 178l: 0.37 g, ~100%: *m/z* 367 (100%), [M+H]⁺.

Compound 178m: 0.111 g, 82%: *m/z* 347 [M+H]⁺.

20 **Compound 178n:** 0.24 g, 83%: *m/z* 347 (100%), [M+H]⁺.

Compound 178o: 0.097 g, 45%: *m/z* 347 (100%), [M+H]⁺.

Compound 179a: Compound **178a** (18 mg, 0.06 mmol) was dissolved in a 3:1 MeOH/THF mixture (1.6 mL), and 30% sodium methoxide (0.066 mL, 1.18 mmol) was added. The reaction mixture was stirred at 55 °C for 5.5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄, and the reaction mixture was concentrated. The residue was extracted with

25

EtOAc and washed with brine, then dried with MgSO₄ and concentrated to give the compound **179a** (13.3 mg, 74%).

Table 12: Compounds 179b-179o (Scheme 31).

Compound Name	R	178b-o mmol	MeONa in MeOH (30%w/w, mL)	MeOH (mL)	Yield (%)
179b	Me	0.45	Not given	Not given	Quantitative
179c	<i>i</i> -Pr	0.588	0.55	20	77
179d	H	0.625	0.60	20	76
179e	Ph	0.711	0.67	10	92
179f	<i>t</i> -Bu	0.464	0.44	10	81
179g	CF ₃	0.518	0.49	10	80
179h	4-Cl-Ph	0.392	0.37	10	92
179i	2-Cl-Ph	0.82	0.77	20	68
179j	3-Me-Ph	0.369	0.35	10	90
179k	4-MeO-Ph	0.362	0.34	10	91
179l	Me-thiazole	1.02	0.96	20	82
179m	3-pyridyl	0.320	0.30	10	72
179n	4-pyridyl	0.71	0.66	20	Quantitative
179o	2-pyridyl	0.28	0.27	25	65

General method J: Compound **178b-o** (see Table 12 for the amount) was taken up in MeOH (see Table 12 for the amount), and 30% NaOMe in MeOH (see Table 12 for the amount) was added. The mixture was stirred under N₂ at 50 °C for 2 h, then at room temperature overnight. The reaction mixture was concentrated. The residue was taken up in EtOAc and washed with saturated NaHCO₃ (aq), saturated NaCl (aq), then dried with MgSO₄ and concentrated to give the corresponding derivatives:

Compound 179b: 0.13 g, quantitative: *m/z* 284 [M+H]⁺.

Compound 179c: 0.141 g, 77%: *m/z* 312 [M+H]⁺.

Compound 179d: 0.128 g, 76%: *m/z* 270 [M+H]⁺.

Compound 179e: 0.225 g, 92%: *m/z* 346 [M+H]⁺.

Compound 179f: 0.123 g, 81%: *m/z* 326 [M+H]⁺.

Compound 179g: 0.140 g, 80%: *m/z* 338 [M+H]⁺.

Compound 179h: 0.137 g, 92%: *m/z* 380, 382 (3:1) [M+H]⁺.

Compound 179i: 0.21 g, 68%: m/z 380/382 (100/52%) $[M+H]^+$.

Compound 179j: 0.119 g, 90%: m/z 360 $[M+H]^+$.

Compound 179k: 0.123 g, 91%: m/z 376 $[M+H]^+$.

Compound 179l: 0.31 g, 82%: m/z 367 (100%) $[M+H]^+$.

5 **Compound 179m:** 0.080 g, 72%: m/z 347 $[M+H]^+$.

Compound 179n: 0.25 g, >100%: m/z 347 (100%) $[M+H]^+$.

Compound 179o: 0.063 g, 65%: m/z 347 (100%) $[M+H]^+$.

Compound TX63528: Compound **179a** (13.3 mg, 0.044 mmol) was dissolved in dry DMF (0.26 mL), and the solution was cooled to 0 °C. 10 Dibromodimethylhydantoin (8.0 mg, 0.028 mmol) was added, and the reaction stirred at 0 °C until the starting material was consumed as reported by thin layer chromatography. Then, pyridine (0.034 mL, 0.416 mmol) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture 15 was extracted with EtOAc and washed with brine, then dried with $MgSO_4$ and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc/Hexanes) to give compound **TX63528** (6.5 mg, 50%). m/z 298 $[M+H]^+$.

Table 13: Compounds of Scheme 31.

Compound Name	R	179b-o (mmol)	DBDMH (mmol)	Pyridine (mL)	Yield (%)
TX63468	Me	0.45	Not given	Not given	51
TX63534	<i>i</i> -Pr	0.454	0.273	0.37	38
TX63542	H	0.478	0.29	0.37	54
TX63552	Ph	0.652	0.392	0.53	51
TX63561	<i>t</i> -Bu	0.377	0.227	0.30	44
TX63567	CF ₃	0.415	0.248	0.34	38
TX63582	4-Cl-Ph	0.361	0.217	0.30	35
TX63612	2-Cl-Ph	0.56	0.28	0.45	67
TX63583	3-Me-Ph	0.330	0.199	0.27	35
TX63590	4-MeO-Ph	0.328	0.196	0.27	38
TX63628	Me-thiazole	0.84	0.42	0.70	23
TX63586	3-pyridyl	0.232	0.140	0.20	26
TX63636	4-pyridyl	0.71	0.35	0.60	51

Compound Name	R	179b-o (mmol)	DBDMH (mmol)	Pyridine (mL)	Yield (%)
TX63641	2-pyridyl	0.18	0.091	0.15	25

General method K: Compound **179b-o** (see Table 13 for the amount) was dissolved in dry DMF (10 mL), and the solution was cooled to 0 °C under N₂. Dibromodimethylhydantoin (DBDMH) (see Table 13 for the amount) was added, and the reaction stirred at 0 °C for 2 h. Pyridine (see Table 13 for the amount) was added, and the reaction was allowed to warm to room temperature. The reaction mixture was stirred at 50 °C for 16 h. After cooling to room temperature, the reaction mixture was concentrated. The residue was extracted with EtOAc and washed with saturated NaHCO₃ (aq), saturated KH₂PO₄ (aq), saturated NaCl (aq), then dried with MgSO₄ and concentrated to give the corresponding derivatives:

Compound TX63468: 65 mg g, 51%: ¹H NMR (400 MHz, CDCl₃) δ 8.88 (s, 1H), 8.44 (s, 1H), 3.00 (dd, 1H, *J* = 6.3, 17.2 Hz), 2.85 (ddd, 1H, *J* = 7.6, 11.4, 17.2 Hz), 2.73 (s, 3H), 2.21 (dd, 1H, *J* = 2.2, 12.5 Hz), 2.06 (m, 1H), 1.96 (m, 1H), 1.48 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H); *m/z* 282 [M+H]⁺.

Compound TX63534: 53 mg, 38%: ¹H NMR (500 MHz, CDCl₃) δ 8.88 (s, 1H), 8.48 (s, 1H), 3.18–3.27 (m, 1H), 3.00 (dd, 1H, *J* = 15.0, 10.0 Hz), 2.81–2.91 (m, 1H), 2.24 (dd, 1H, *J* = 10.0, 5.0 Hz), 2.03–2.09 (m, 1H), 1.90–2.01 (m, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H); *m/z* 310 [M+H]⁺.

Compound TX63542: 56.8 mg, 54%: ¹H NMR (500 MHz, CDCl₃) δ 9.04 (br s, 1H), 8.79 (s, 1H), 8.55 (br s, 1H), 3.02 (dd, 1H, *J* = 6.1, 17.5 Hz), 2.92–2.84 (m, 1H), 2.20 (dd, 1H, *J* = 1.8, 12.6 Hz), 2.06–2.02 (m, 1H), 1.93 (dddd, 1H, *J* = 6.5, 12.0, 12.3, 12.6 Hz), 1.45 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H); *m/z* 268 [M+H]⁺.

Compound TX63552: 114 mg, 51%: ¹H NMR (500 MHz, CDCl₃) δ 8.95 (s, 1H), 8.57 (s, 1H), 8.43 (m, 2H), 7.50 (m, 3H), 3.03 (dd, 1H, *J* = 6.1, 17.5 Hz), 2.92–2.85 (m, 1H), 2.25 (d, 1H, *J* = 12.4 Hz), 2.08–2.01 (m, 1H), 1.99–1.92 (m, 1H), 1.51 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); *m/z* 344 [M+H]⁺.

Compound TX63561: 54 mg, 44%: ¹H NMR (500 MHz, CDCl₃) δ 8.81 (s, 1H), 8.44 (s, 1H), 2.95 (dd, 1H, *J* = 6.0, 17.3 Hz), 2.80 (dddd, 1H, *J* = 7.3, 8.8, 8.9, 11.4 Hz), 2.20 (dd, 1H, *J* = 1.9, 12.5 Hz), 2.03–1.99 (m, 1H), 1.91 (dddd, 1H, *J* = 6.4, 12.3, 12.5, 12.6 Hz), 1.43 (s, 3H), 1.39 (s, 9H), 1.28 (s, 3H), 1.23 (s, 3H); *m/z* 324 [M+H]⁺.

Compound TX63567: 52 mg, 38%: ^1H NMR (500 MHz, CDCl_3) δ 8.70 (s, 1H), 8.67 (s, 1H), 3.12 (dd, 1H, $J = 6.1, 18.1$ Hz), 2.96 (dddd, 1H, $J = 7.5, 9.1, 9.3, 10.9$ Hz), 2.23 (dd, 1H, $J = 2.1, 12.8$ Hz), 2.12–2.08 (m, 1H), 1.98 (dddd, 1H, $J = 6.6, 12.6, 13.0, 13.3$ Hz), 1.49 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H); m/z 336 $[\text{M}+\text{H}]^+$.

5 **Compound TX63582:** 47 mg, 35%: ^1H NMR (500 MHz, CDCl_3) δ 8.90 (s, 1H), 8.57 (s, 1H), 8.39 (d, 2H, $J = 8.5$ Hz), 7.46 (d, 2H, $J = 8.5$ Hz), 3.04 (dd, 1H, $J = 5.8, 17.4$ Hz), 2.92–2.85 (m, 1H), 2.24 (dd, 1H, $J = 1.8, 12.5$ Hz), 2.08–2.04 (m, 1H), 2.01–1.93 (m, 1H), 1.51 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); m/z 378, 380 (100%:38%) $[\text{M}+\text{H}]^+$.

10 **Compound TX63612:** 140 mg, 67%: ^1H NMR (500 MHz, CDCl_3) δ 8.88 (s, 1H), 8.66 (s, 1H), 7.79–7.81 (m, 1H), 7.51–7.54 (m, 1H), 7.39–7.42 (m, 2H), 3.08 (dd, 1H, $J = 20, 5$ Hz), 2.90–2.97 (m, 1H), 2.28 (dd, 1H, $J = 15, 2.5$ Hz), 1.95–2.11 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H); m/z 378/380 (100/39%) $[\text{M}+\text{H}]^+$.

15 **Compound TX63583:** 30 mg, 35%: ^1H NMR (500 MHz, CDCl_3) δ 8.95 (s, 1H), 8.56 (s, 1H), 8.23 (br s, 2H), 7.44–7.30 (m, 2H), 3.04–3.01 (m, 1H), 2.91–2.84 (m, 1H), 2.47 (s, 3H), 2.25 (d, 1H, $J = 12.1$ Hz), 2.07–1.95 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H); m/z 358 $[\text{M}+\text{H}]^+$.

20 **Compound TX63590:** 47 mg, 38%: ^1H NMR (400 MHz, CDCl_3) δ 8.98 (s, 1H), 8.55 (s, 1H), 8.43 (d, 2H, $J = 10.0$ Hz), 7.05 (d, 2H, $J = 5.0$ Hz), 3.92 (s, 3H), 3.05 (dd, 1H, $J = 20.0, 5.0$ Hz), 2.85–2.95 (m, 1H), 2.28 (dd, 1H, $J = 10.0, 5.0$ Hz), 1.94–2.13 (m, 2H), 1.54 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H); m/z 374 $[\text{M}+\text{H}]^+$.

25 **Compound TX63628:** 70 mg, 23%: ^1H NMR (500 MHz, CDCl_3) δ 8.93 (s, 1H), 8.65 (s, 1H), 8.22 (s, 1H), 3.09 (dd, 1H, $J = 6.2, 6.1$ Hz), 2.93 (m, 1H), 2.86 (s, 3H), 2.28 (dd, 1H, $J = 1.8, 1.8$ Hz), 2.03 (m, 2H), 1.55 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H); m/z 365 (100%) $[\text{M}+\text{H}]^+$.

30 **Compound TX63586:** 21 mg, 26%: ^1H NMR (500 MHz, CDCl_3) δ 9.69 (s, 1H), 8.91 (dt, 1H, $J = 1.5, 8.0$ Hz), 8.86 (s, 1H), 8.75 (dd, 1H, $J = 1.0, 4.8$ Hz), 8.63 (s, 1H), 7.62 (dd, 1H, $J = 5.0, 7.9$ Hz), 3.08 (dd, 1H, $J = 6.0, 17.9$ Hz), 2.93 (dddd, 1H, $J = 7.3, 9.0, 9.0, 11.0$ Hz), 2.25 (dd, 1H, $J = 2.3, 12.6$ Hz), 2.11–2.06 (m, 1H), 2.02–1.94 (dddd, 1H, $J = 6.5, 12.5, 12.9, 13.5$ Hz), 1.52 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); m/z 345 $[\text{M}+\text{H}]^+$.

Compound TX63636: 120 mg, 51%: ^1H NMR (500 MHz, CDCl_3) δ 8.94 (s, 1H), 8.83 (d, 2H, $J = 5.14$), 8.68 (s, 1H), 8.32 (d, 2H, $J = 5.45$), 3.12 (dd, 1H, $J = 6.17$,

11.64, 6.04 Hz), 3.02-2.92 (m, 1H), 2.30 (dd, 1H, $J = 1.93, 10.6, 2.03$), 2.17-1.97 (m, 2H), 1.57 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H); m/z 345 (100%) $[M+H]^+$.

Compound TX63641: 15 mg, 25%: ^1H NMR (500 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.87 (s, 1H), 8.76 (s, 1H), 8.55 (d, 1H, $J = 7.7$), 7.92 (t, 1H, 7.2, 7.2), 7.49 (t, 1H, $J = 5.25, 5.7$), 3.14 (dd, 1H, $J = 5.99, 12.01, 5.25$ Hz), 3.04-2.91 (m, 1H), 2.31 (d, 1H, $J = 11.88$), 2.18-1.94 (m, 2H), 1.57 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H); m/z 345 (100%), $[M+H]^+$.

Compound 180: A solution of **25** (1.4 g, 5.5 mmol) in THF (10 mL) was added to a refluxing mixture of dimethyl carbonate (6 equiv.) and NaH (excess) in THF (10 mL). The reaction was stirred at reflux for 3 h. The reaction mixture was cooled to room temperature, quenched KH_2PO_4 (aq) and extracted with EtOAc, then washed with brine, dried with $MgSO_4$ and concentrated to give compound **180** (1.5 g, 87%) as a solid. m/z 311 $[M+H]^+$.

Compound 181: A solution of acetamide hydrochloride (5.3 g, 55 mmol) and piperidine (2.4 g, 28 mmol) in *i*-PrOH (20 mL) was stirred at room temperature for 15 min, then compound **184** (1.5 g, 4.8 mmol) was added. The reaction mixture was heated at reflux for 2 d, then concentrated. The crude residue was purified by column chromatography (silica gel, 15 to 65 % EtOAc in Hexanes) to give **181** (0.95 g, 62%) as a solid. m/z 319 $[M+H]^+$.

Compound 182: Compound **185** (468 mg, 1.47 mmol) was taken up in $CHCl_3$ (15 mL) and the solution cooled to 0 °C. Triethylamine (1.5 equiv.) and Tf_2O (1.1 equiv.) were added, and the reaction was stirred at 0 °C for 2 h. The reaction mixture was washed with water, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 15 % EtOAc in Hexanes) to give **182** (548 mg, 83%) as a solid. m/z 451 $[M+H]^+$.

Compound 183: A mixture of compound **182** (548 mg, 1.22 mmol), phenylboronic acid (1.2 equiv.), Ph_3P (0.36 equiv.), K_3PO_4 (3 equiv.) and DME was sparged with N_2 for 10 min. $Pd(OAc)_2$ (0.18 equiv.) was added and sparging with N_2 was continued for 10 min. The reaction was heated to 85 °C for 16 h. The reaction mixture was filtered and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 35 % EtOAc in Hexanes) to give compound **183** (380 mg, 83%) as an off-white solid: m/z 379 $[M+H]^+$.

Compound 184: Compound **183** (0.38 g, 1.0 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred overnight at room

temperature. The reaction mixture was then concentrated. The reaction mixture was diluted with saturated NaHCO_3 and extracted with EtOAc (2×25 mL), then dried with MgSO_4 and concentrated to give compound **184** (0.36 g, quantitative) as a solid. m/z 335 $[\text{M}+\text{H}]^+$.

5 **Compound 185:** Compound **184** (0.36 g, 1.0 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched KH_2PO_4 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 and concentrated to give compound **184** (0.37 g, quantitative) as a solid. m/z 363 $[\text{M}+\text{H}]^+$.

10 **Compound 186:** A mixture of hydroxylamine hydrochloride and **185** (0.37 g, 1.0 mmol) in ethanol was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with water and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **186** (0.37 g, quantitative) as a solid. m/z 360 $[\text{M}+\text{H}]^+$.

15 **Compound 187:** Compound **186** (0.37 g, 1.0 mmol) was dissolved in a 2/1 THF/methanol mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h. The reaction mixture was concentrated and quenched by addition of saturated KH_2PO_4 . The mixture was extracted with EtOAc and washed with brine, then dried with MgSO_4 and concentrated to give compound **187** (0.37 g, quantitative) as a solid. m/z 360 $[\text{M}+\text{H}]^+$.

20 **Compound TX63529:** Compound **187** (0.37 g, 1.0 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 2 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 25 % EtOAc in Hexanes) to give compound **TX63529** (0.24 g, 67%) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.86 (s, 1H), 7.55 (m, 2H), 7.50 (s, 3H), 2.88 (m, 1H), 2.76 (dd, 1H, $J = 5.8, 17.0$ Hz, 1H), 2.67 (s, 3H), 2.36 (dd, 1H, $J = 2.0, 12.4$ Hz), 1.92 (m, 1H), 1.83 (m, 1H), 1.47 (s, 3H), 1.21 (s, 3H), 1.14 (s, 3H); m/z 358 $[\text{M}+\text{H}]^+$.

30 **Compound 188:** A mixture of compound **26** (148 mg, 0.53 mmol) and urea (2 equiv.) in dioxane was stirred at reflux for 3 d. The reaction mixture was

concentrated. The residue was taken up in MeOH, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The reaction mixture was stirred at reflux for 3 d, then cooled to room temperature, diluted with acetic acid (0.2 mL) and water (2 mL), and concentrated. The residue was diluted with 1 N HCl (aq) and extracted with EtOAc, then dried with MgSO₄ and concentrated to give **188** as a brown oil. *m/z* 305 [M+H]⁺.

Compound 189: Compound **188** was taken up in MeOH, and 3 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated, extracted with EtOAc (50 mL), and washed with saturated NaHCO₃, then dried with MgSO₄ and concentrated to give compound **189** (98 mg, 71%) as a solid. *m/z* 261 [M+H]⁺.

Compound 190: Compound **189** (98 mg, 0.38 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature, then additional ethyl formate (5 mL) was added and the reaction was heated to 50 °C for 2 h. The reaction mixture was extracted with EtOAc and washed with KH₂PO₄ (aq), then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25–100% EtOAc/Hexanes) to give compound **190** (52.7 mg, 49%) as a solid. *m/z* 289 [M+H]⁺.

Compound 191: A solution of 0.1 N hydroxylamine hydrochloride (aq.) was added to compound **190** (52.7 mg, 0.18 mmol). A 9:1 mixture of ethanol/water was added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, then dried with MgSO₄ and concentrated to give compound **191** as a solid. *m/z* 286 [M+H]⁺.

Compound 192: Compound **191** was dissolved in a 3:1 MeOH/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of HOAc and concentrated. The crude residue was purified by column chromatography (silica gel, 10% MeOH/CH₂Cl₂) to give compound **192** (7.8 mg, 15%) as a solid. *m/z* 286 [M+H]⁺.

Compound TX63553: Compound **192** (7.8 mg, 0.027 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed

(approximately 30 min), as reported by thin layer chromatography. Pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with
5 MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 8% MeOH/CH₂Cl₂), then preparative thin layer chromatography (silica gel, EtOAc) to give compound **TX63553** (2.4 mg, 31%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ 8.74 (s, 1H), 7.63 (s, 1H), 7.23 (br s, 1H), 2.84 (dd, 1H, *J* = 6.5, 16.6 Hz), 2.71–2.64 (m, 1H), 2.14 (dd, 1H, *J* = 2.0, 12.5 Hz), 1.94–1.85 (m, 2H), 1.47 (s,
10 3H), 1.26 (s, 3H), 1.19 (s, 3H); *m/z* 284 [M+H]⁺.

Compound 193: A solution of compound **129** (898 mg, 3.37 mmol), acetamide hydrochloride (3.2 g, 34 mmol), and piperidine (2.0 ml, 20 mmol) in *i*-PrOH (15 mL) was heated at reflux for 2 d, then concentrated. The residue was taken
15 up in CHCl₃, washed with 10% NH₄OH (aq) and brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give **193** (464 mg, 48%) as a solid. *m/z* 289 [M+H]⁺.

Compound 194: Compound **193** (464 mg, 1.61 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred 16 h at room temperature. The reaction mixture was concentrated, diluted with 10% NH₄OH (aq),
20 and extracted with CHCl₃, then washed with brine, dried with MgSO₄, and concentrated to give compound **193** (371 mg, 94%) as a solid. *m/z* 245 [M+H]⁺.

Compound 195: Compound **194** (371 mg, 1.52 mmol) was taken up in benzene (20 mL), then ethyl formate (1.25 mL) and 30% sodium methoxide (30 wt% solution in MeOH) were added. The mixture was stirred 16 h at room temperature,
25 then concentrated. The mixture was diluted with KH₂PO₄ (aq) and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated to give compound **194** (371 mg, 90%) as a solid. *m/z* 273 [M+H]⁺.

Compound 196: A mixture of hydroxylamine hydrochloride and **195** (371 mg, 1.36 mmol) in ethanol was stirred for 16 h at 50 °C. After cooling to room
30 temperature, the reaction mixture was concentrated. The residue was diluted with saturated NaHCO₃ (aq) and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated to give compound **196** (361 mg, 98%) as a solid. *m/z* 270 [M+H]⁺.

Compound 197: Compound **196** (361 mg, 1.34 mmol) was dissolved in methanol, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated and diluted with EtOAc, then washed with saturated KH_2PO_4 and brine, dried with MgSO_4 , and concentrated to give compound **197** (287 mg, 80%) as a solid. m/z 270 $[\text{M}+\text{H}]^+$.

Compound TX63554: Compound **197** (287 mg, 0.80 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 1 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C for 16 h. The reaction mixture was concentrated and diluted with EtOAc, then washed with saturated KH_2PO_4 and brine, dried with MgSO_4 , and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **TX63554** (145 mg, 51%) as a solid. ^1H NMR (500 MHz, CDCl_3) δ 8.89 (s, 1H), 8.44 (s, 1H), 2.96 (dd, 1H, $J = 6.8, 17.5$ Hz), 2.86 (ddd, 1H, $J = 7.0, 10.9, 17.1$ Hz), 2.74 (s, 3H), 2.60 (qd, 1H, $J = 6.7, 13.1$ Hz), 2.15 (m, 2H), 1.82 (m, 1H), 1.43 (s, 3H), 1.33 (d, 3H, $J = 6.7$ Hz); m/z 268 $[\text{M}+\text{H}]^+$.

Compound 198: A solution of compound **129** (330 mg, 1.24 mmol), acetamide hydrochloride (1.94 g, 12.4 mmol), and piperidine (0.74 mL, 7.5 mmol) in *i*-PrOH (10 mL) was heated at 85 °C for 4 d, then concentrated. The residue was taken up in CHCl_3 , washed with 10% NH_4OH (aq) and brine, then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 20 % EtOAc in Hexanes) to give **198** (260 mg, 60%) as a solid. m/z 351 $[\text{M}+\text{H}]^+$.

Compound 199: Compound **198** (260 mg, 0.74 mmol) was taken up in methanol, and 3 N HCl (aq) was added. The mixture was stirred 16 h at room temperature. The reaction mixture was concentrated, diluted with 10% NH_4OH (aq), and extracted with CHCl_3 , then washed with brine, dried with MgSO_4 , and concentrated to give compound **199** (217 mg, 95%) as a white solid. m/z 307 $[\text{M}+\text{H}]^+$.

Compound 200: Compound **199** (217 mg, 0.71 mmol) was taken up in benzene (20 mL), then ethyl formate (1.25 mL) and 30% sodium methoxide (30 wt% solution in MeOH) were added. The mixture was stirred 16 h at room temperature, then concentrated. The mixture was diluted with KH_2PO_4 (aq) and extracted with

EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **200** (216 mg, 91%) as a solid. m/z 335 $[\text{M}+\text{H}]^+$.

Compound 201: A mixture of hydroxylamine hydrochloride and **200** (216 mg, 0.65 mmol) in ethanol was stirred for 4 h at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted EtOAc, washed with saturated NaHCO_3 (aq) and brine, dried with MgSO_4 , and concentrated to give compound **200** (190 mg, 89%) as a solid. m/z 332 $[\text{M}+\text{H}]^+$.

Compound 202: Compound **201** (190 mg, 0.57 mmol) was dissolved in methanol, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and diluted with EtOAc, then washed with saturated KH_2PO_4 and brine, dried with MgSO_4 , and concentrated to give compound **201** (228 mg, quantitative) as a solid. m/z 332 $[\text{M}+\text{H}]^+$.

Compound TX63569: Compound **202** (228 mg, 0.57 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 1 h), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C for 16 h. The reaction mixture was concentrated and diluted with EtOAc, then washed with saturated KH_2PO_4 and brine, dried with MgSO_4 , and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in Hexanes) to give compound **TX63569** (68 mg, 36%) as a solid. ^1H NMR (500 MHz, CDCl_3) δ 9.01 (s, 1H), 8.62 (s, 1H), 8.49 (m, 2H), 7.55 (m, 3H), 3.04 (dd, 1H, $J = 6.5, 17.8$ Hz), 2.94 (ddd, 1H, $J = 7.3, 11.3, 17.8$ Hz), 2.64 (qd, 1H, $J = 6.7, 12.7$ Hz), 2.22 (m, 2H), 1.88 (m, 1H), 1.51 (s, 3H), 1.37 (d, 3H, $J = 6.7$ Hz); m/z 330 $[\text{M}+\text{H}]^+$.

Compound 203: Compound **25** (0.297 g, 1.18 mmol) was taken up in DCM (50 mL) and $\text{MgBr}\cdot\text{Et}_2\text{O}$ (0.776 g, 3.0 mmol) was added followed by *i*- Pr_2NEt (0.42 mL, 2.3 mmol). The reaction mixture was stirred at room temperature for about 40 minutes, during which time the reaction gradually turned orange. Benzoyl chloride (0.347 g, 2.44 mmol) in DCM (3 mL) was added dropwise and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated aqueous NaHCO_3 solution (10 mL), the layers were separated, and the organic layer was dried over MgSO_4 , filtered and concentrated to a reddish oil. The product was present by

mass spectral analysis, MS: m/z $[M+H]^+$ 357.0. This crude material was used directly in the next step. The residue was taken up in EtOH (16 mL), and nitrogen gas was bubbled through the solution for 5 minutes. Phenylhydrazine (0.5 mL, 5.08 mmol) was added by syringe and the tightly sealed vial was heated overnight to 80 °C with stirring. After cooling to room temperature the reaction mixture was concentrated to dryness, taken up in EtOAc (80 mL), washed with saturated aqueous KH_2PO_4 (15 mL) and saturated aqueous $NaHCO_3$ solution (15 mL), dried over $MgSO_4$, filtered and concentrated to a red oil. The product was present by mass spec, MS: m/z $[M+H]^+$ 429.1. This material was used directly in the next step. The crude ketal mixture was taken up in MeOH (20 mL) and 1N HCl (4 mL) was added. The reaction was stirred overnight at room temperature, then concentrated and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to a red oil/solid. The oil/solid was chromatographed 3 successive times on silica gel (230–400 mesh, 26 g) using 20% Hexanes/EtOAc to afford the more polar isomer (**203**, 94.4 mg) with a minor less polar impurity. MS: m/z $[M+H]^+$ 385.1.

Compound 204: Compound **203** (91 mg, 0.237 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH_2PO_4 (aq) and extracted with EtOAc, then dried with $MgSO_4$ and concentrated to give compound **204** (90 mg). m/z $[M+H]^+$ 413.1.

Compound 205: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **203** (90 mg, 0.22 mmol). A 9:1 mixture of EtOH/ H_2O was added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, then dried with $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (230–400 mesh, 10 g) using 20% Hexanes/EtOAc as a faintly yellow glass to give compound **205** (22.8 mg). m/z $[M+H]^+$ 410.1.

Compound 206: Compound **205** (22.8 mg, 0.054 mmol) was dissolved in a 3:1 MeOH/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The reaction mixture was stirred at 55 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 , and the reaction mixture was concentrated. The residue was extracted with EtOAc and washed with brine, then dried with $MgSO_4$ and concentrated. The crude residue

was purified by column chromatography (silica gel, 50% EtOAc/Hexanes) to give compound **206** (22 mg) as an off-white foam. This material was used directly in the next step.

Compound TX63605: Compound **206** (22 mg, 0.038 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was chromatographed twice on silica gel using 3:1 Hexanes/EtOAc then purified by preparative thin layer chromatography using 3:1 Hexanes/EtOAc to give **TX63605** (4.5 mg) as a glass. ¹H NMR (500 MHz, CDCl₃) δ 7.73-7.76 (m, 2H), 7.36-7.60 (m, 9H), 3.00-3.08 (m, 1H), 2.85-2.95 (m, 1H), 2.41-2.44 (m, 1H), 1.92-2.10 (m, 2H), 1.62 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H); *m/z* [M+H]⁺ 408.1.

Compound 208: Compound **207** (4.0 g, 19 mmol) was taken up in *t*-BuOH, and a solution of KO*t*-Bu in *t*-BuOH was added. The mixture was stirred at room temperature for 20 min and iodomethane was added. The reaction mixture was stirred for 45 min at room temperature, quenched with saturated NH₄Cl (aq), and concentrated. The mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 10 % EtOAc in Hexanes) to give compound **208** (2.5 g, 55%) as a pale yellow liquid: *m/z* 177 (M-CH₃OCH₂OH).

Compound 209: Compound **208** (2.5 g, 10 mmol) was taken up in EtOAc under N₂ and 10% Pd/C added. The flask was rigorously purged with H₂ and stirred overnight at room temperature. The reaction mixture was filtered and concentrated to give compound **209** (2.5 g, 99%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ 4.70 (d, 1H, *J* = 7 Hz), 4.61 (d, 1H, *J* = 7 Hz), 3.65 (t, 1H, *J* = 6 Hz), 3.38 (s, 3H), 2.58 (td, 1H, *J* = 7, 17 Hz), 2.25 (td, 1H, *J* = 7, 17 Hz), 1.91 (m, 3H), 1.77 (m, 2H), 1.53 (m, 1H), 1.23 (s, 6H), 1.10 (m, 1H), 1.01 (s, 3H).

Compound 210: A mixture of compound **209** (2.5 g, 10 mmol), ethylene glycol, and *p*-toluenesulfonic acid hydrate in toluene was heated to reflux for 3 h with azeotropic removal of water. The reaction mixture was cooled to room temperature,

washed with saturated NaHCO_3 (aq) and brine, then dried with MgSO_4 and concentrated. The crude residue was taken up in CH_2Cl_2 and PDC (1.5 equiv.) was added. The reaction mixture was stirred at room temperature for 22 h. The reaction mixture was filtered through Celite (eluted with CH_2Cl_2) and concentrated. The crude residue was purified by column chromatography (silica gel, 10 % EtOAc in Hexanes) to give compound **210** (1.8 g, 73%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 3.90 (m, 4H), 2.33 (m, 1H), 2.10 (m, 2H), 1.94 (m, 1H), 1.85 (m, 1H), 1.72 (m, 2H), 1.49 (m, 1H), 1.26 (m, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.88 (s, 3H).

Compound 211: Compound **210** (0.81 g, 3.4 mmol) was taken up in ethyl formate (8.2 mL), cooled to 0 °C, and 30% sodium methoxide (30 wt% solution in MeOH, 9.6 mL) was added. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with *t*-BuOMe, cooled to 0 °C, and quenched with concentrated HCl (4.25 mL). The mixture was diluted with water and extracted with EtOAc, then dried with MgSO_4 and concentrated to give compound **211** (0.92 g, quantitative) as a viscous oil. m/z 267 $[\text{M}+\text{H}]^+$.

Compound 212: A mixture of **211** (0.90 g, 3.4 mmol) and methylhydrazine (0.20 g, 4.4 mmol) in ethanol (20 mL) was heated to 65 °C for 4 h. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 50 to 75 % EtOAc in Hexanes) to give **212** (0.25 g, 27%) as a viscous oil. m/z 277 $[\text{M}+\text{H}]^+$.

Compound 213: Compound **212** (0.25 g, 0.91 mmol) was taken up in THF, and 1 N HCl (aq) was added. The mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with saturated NaHCO_3 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **213** (0.19 g, 90%) as a solid. m/z 233 $[\text{M}+\text{H}]^+$.

Compound 214: A solution of compound **213** (0.27 g, 1.2 mmol) in THF was added to a -78 °C solution of LDA (2.5 equiv.) in THF. The reaction was stirred at -78 °C for 30 min, then a solution of TsCN (1.3 equiv.) in THF was added. The reaction was stirred at -78 °C for an additional 30 min, then quenched with saturated NH_4Cl (aq) and warmed to room temperature. The reaction mixture was diluted with water and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in CH_2Cl_2) to give compound **214** (0.24 g, 80%) as a solid. m/z 258 $[\text{M}+\text{H}]^+$.

Compound TX63436: Compound **214** (90 mg, 0.35 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C for 1 h, then warmed to room temperature and stirred for 1 h. Then, pyridine was added, and the reaction was stirred at 60 °C overnight. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate and washed with 1 N HCl (aq), saturated NaHCO₃ (aq), and brine, then dried with MgSO₄ and concentrated. The crude residue was recrystallized from EtOAc to give **TX63436** (41 mg, 46%) as a crystalline solid. ¹H NMR (500 MHz, CDCl₃) δ 7.24 (s, 1H), 7.15 (s, 1H), 3.91 (s, 3H), 2.95 (br t, 1H, *J* = 10 Hz), 2.82 (dd, 1H, *J* = 8, 15 Hz), 2.18 (dd, 1H, *J* = 10, 15 Hz), 1.81 (s, 3H), 1.39 (s, 3H), 1.24 (s, 3H); *m/z* 256 [M+H]⁺.

Compound 216: Compound **215** (2.8 g, 9.5 mmol) was taken up in THF (75 mL) under N₂ and 10% Pd/C (0.25 g) added. The reaction was cooled to 0 °C and the flask was rigorously purged with H₂. The reaction was stirred at 0 °C for 8 h, then stirred overnight at room temperature. The flask was again cooled to 0 °C and an additional portion of 10% Pd/C (0.20 g) was added. The flask was rigorously purged with H₂ and the reaction was stirred at 0 °C for 8 h, then stirred 3 d at room temperature. The reaction mixture was filtered and concentrated. The residue was taken up in MeOH (50 mL) and 30% sodium methoxide (30 wt% solution in MeOH, 0.5 mL) was added. The reaction was stirred at room temperature overnight and then concentrated. The mixture was diluted with saturated NH₄Cl (aq) and extracted with EtOAc, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 3 to 5 % EtOAc in Hexanes) to give compound **216** (1.18 g, 42%) as an oil. *m/z* 297 [M+H]⁺.

Compound 217: A mixture of compound **216** (0.95 g, 3.2 mmol), ethylene glycol, and *p*-toluenesulfonic acid hydrate in toluene was heated to reflux for 3 h with azeotropic removal of water. The reaction mixture was cooled to room temperature, diluted with saturated NaHCO₃ (aq), and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated to give compound **217** (1.09 g, quantitative) as an oil. *m/z* 342 [M+H]⁺.

Compound 218: Compound **217** (1.33 g, 3.91 mmol) was taken up in THF, and TBAF hydrate (1.1 equiv.) was added. The reaction was stirred at room temperature for 3 d, with additional portions of TBAF hydrate (0.55 equiv.) being added after 8 and 24 h. The reaction mixture was diluted with saturated NaHCO₃ (aq)

and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated. The crude residue was purified by column chromatography (silica gel, 40 % EtOAc in Hexanes) to give compound **218** (0.83 g, 94%) as a solid. m/z 227 [M+H]⁺.

5 **Compound 219:** Compound **218** (0.83 g, 3.67 mmol) was taken up in CH₂Cl₂ and PDC (1.5 equiv.) was added. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through Celite (eluted with CH₂Cl₂) and concentrated. The crude residue was purified by column chromatography (silica gel, 10 % EtOAc in Hexanes) to give compound **219** (0.82 g, quantitative) as a solid. m/z 225 [M+H]⁺.

10 **Compound 220:** Compound **219** (0.80 g, 3.6 mmol) was taken up in ethyl formate, cooled to 0 °C, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated NH₄Cl (aq) and extracted with EtOAc, 15 then washed with brine, dried with MgSO₄, and concentrated to give compound **220** (0.90 g, quantitative) as a solid. m/z 253 [M+H]⁺.

20 **Compound 221:** A mixture of **220** (0.70 g, 2.8 mmol) and methylhydrazine (0.32 g, 6.9 mmol) in ethanol (13 mL) was heated to 65 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 80 to 100 % EtOAc in Hexanes) to give an off-white solid. The residue was taken up in THF, and 1 N HCl (aq) was added. The mixture was stirred for 3 d at room temperature. The reaction mixture was quenched with saturated NaHCO₃ (aq) and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated to give compound **221** (0.50 g, 83%) as a solid. m/z 219 25 [M+H]⁺.

30 **Compound 222:** Compound **221** (225 mg, 1.03 mmol) was taken up in ethyl formate, cooled to 0 °C, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated KH₂PO₄ (aq) and extracted with EtOAc, then washed with brine, dried with MgSO₄, and concentrated to give compound **222** (0.28 g, quantitative) as a solid. m/z 247 [M+H]⁺.

Compound 223: Compound **222** (0.28 g, 1.03 mmol) was taken up in a 9/1 mixture of ethanol/water, and hydroxylamine hydrochloride was added. The reaction mixture was stirred overnight at 60 °C. After cooling to room temperature, the

reaction mixture was concentrated. The residue was diluted with saturated NaHCO_3 (aq) and extracted with EtOAc, then dried with MgSO_4 and concentrated to give compound **223** (0.26 g, quantitative) as a solid. m/z 244 $[\text{M}+\text{H}]^+$.

Compound 224: Compound **223** (0.25 g, 1.03 mmol) was dissolved in a 1/1
5 methanol/THF mixture, 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4 and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **224** (0.15 g, 60%) as a solid. m/z 244 $[\text{M}+\text{H}]^+$.

Compound TX63533: Compound **224** (150 mg, 0.62 mmol) was dissolved in
10 dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C for 1 h, then warmed to room temperature and stirred 1h. Then, pyridine was added, and the reaction mixture was then stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted
15 with EtOAc and washed with 1 N HCl (aq), saturated NaHCO_3 (aq), and brine, then dried with MgSO_4 and concentrated. The combined aqueous fractions were extracted with CHCl_3 , which was dried with MgSO_4 and concentrated. The combined crude product was purified by successive column chromatography, first (silica gel, 50 % EtOAc in CH_2Cl_2), then (silica gel, 2 % MeOH in CH_2Cl_2) to give **TX63533** (30 mg,
20 20%) as a solid. ^1H NMR (500 MHz, CDCl_3) δ 8.28 (s, 1H), 7.24 (s, 1H), 3.97 (s, 3H), 2.95 (ddd, 1H, $J = 6.2, 10.8, 13.9$ Hz), 2.86 (qd, 1H, $J = 6.5, 13.7$ Hz), 2.73 (dd, 1H, $J = 6.1, 13.9$ Hz), 2.46 (dd, 1H, $J = 10.8, 13.9$ Hz), 1.36 (s, 3H), 1.33 (d, 3H, $J = 6.6$ Hz); m/z 242 $[\text{M}+\text{H}]^+$.

Compound 225: Compound **216** (0.61 g, 2.1 mmol) was taken up in MeCN,
25 then hexamethyldisilazane (10 equiv) and NaI (5 equiv.) were added and the mixture stirred at room temperature for 5 minutes. The chlorotrimethylsilane (5 equiv.) was added and the solution was stirred at room temperature overnight. The reaction mixture was diluted with saturated NH_4Cl (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated. The residue was taken up in
30 EtOAc, filtered through a short pad of silica (eluted with EtOAc), and concentrated. The residue was taken up in MeCN, $\text{Pd}(\text{OAc})_2$ (2 equiv.) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a short pad of silica (eluted with EtOAc), washed with saturated NaHCO_3 (aq) and brine, dried with MgSO_4 , and concentrated. The crude residue was purified

by column chromatography (silica gel, 10 % EtOAc in Hexanes) to give compound **225** (0.48 g, 79%) as a white solid. m/z 295 $[M+H]^+$.

Compound 226: A solution of compound **225** (0.47 g, 1.6 mmol) in THF was added to a 0 °C solution of KHMDS (2 equiv.) in THF. The solution was stirred at 0 °C for 30 min, then methyl iodide (4 equiv.) was added. The reaction mixture was stirred at 0 °C for 30 min, quenched with saturated NH_4Cl (aq), and extracted with EtOAc, then washed with brine, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 5 to 10 % EtOAc in Hexanes) to give compound **226** (0.40 g, 81%) as a white solid. m/z 309 $[M+H]^+$.

Compound 227: Compound **226** (0.39 g, 1.3 mmol) was taken up in THF under N_2 and 10% Pd/C added. The flask was rigorously purged with H_2 and stirred at room temperature for 3 h. The reaction mixture was filtered and concentrated to give compound **227** (0.39 g, 99%) as an oil. m/z 311 $[M+H]^+$.

Compound 228: Compound **227** (0.39 g, 1.3 mmol) was taken up in CH_2Cl_2 (2 ml), then methylethyldioxolane (3 ml), ethylene glycol (1 drop), and *p*-toluenesulfonic acid (cat.) was added. The solution was stirred at room temperature for 2 d, quenched with saturated $NaHCO_3$ (aq), and extracted with EtOAc, then washed with brine, dried with $MgSO_4$, and concentrated to give compound **228** (0.44 g, 99%) as an oil. m/z 355 $[M+H]^+$.

Compound 229: Compound **228** (0.44 g, 1.3 mmol) was taken up in THF, and a solution of TBAF in THF (1.0 M, 2 ml) was added. The reaction was stirred at room temperature for 4 d, with portions of TBAF hydrate (0.65 equiv.) being added after 24 and 48 h. The reaction mixture was diluted with saturated $NaHCO_3$ (aq) and extracted with EtOAc, then washed with brine, dried with $MgSO_4$, and concentrated. The crude residue was purified by column chromatography (silica gel, 40 % EtOAc in Hexanes) to give compound **229** (0.27 g, 89%) as a solid. m/z 241 $[M+H]^+$.

Compound 230: Compound **229** (0.27 g, 1.1 mmol) was taken up in CH_2Cl_2 and PDC (1.5 equiv.) was added. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through Celite (eluted with CH_2Cl_2) and concentrated. The crude residue was purified by column chromatography (silica gel, 20 % EtOAc in Hexanes) to give compound **230** (0.24 g, 90%) as a solid. m/z 239 $[M+H]^+$.

Compound 231: Compound **230** (0.23 g, 0.97 mmol) was taken up in ethyl formate, cooled to 0 °C, and 30% sodium methoxide (30 wt% solution in MeOH) was

added. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **231** (0.29 g, quantitative) as a solid. m/z 267 $[\text{M}+\text{H}]^+$.

5 **Compound 232:** A mixture of **231** (0.29 g, 0.97 mmol) and methylhydrazine (90 mg, 2.0 mmol) in ethanol (0.5 mL) was heated to 65 °C overnight. The reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 75 % EtOAc in Hexanes) to give a white solid. The residue was taken up in THF, and 1 N HCl (aq) was added. The mixture was stirred
10 for 2 d at room temperature. The reaction mixture was quenched with saturated NaHCO_3 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **232** (0.17 g, 76%) as a solid. m/z 233 $[\text{M}+\text{H}]^+$.

Compound 233: Compound **232** (0.17 g, 0.73 mmol) was taken up in ethyl formate, cooled to 0 °C, and 30% sodium methoxide (30 wt% solution in MeOH) was
15 added. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated KH_2PO_4 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **233** (0.19 g, 96%) as a solid. m/z 261 $[\text{M}+\text{H}]^+$.

Compound 234: Compound **233** (0.19 g, 0.73 mmol) was taken up in a 8/1
20 mixture of ethanol/water, and hydroxylamine hydrochloride was added. The reaction mixture was stirred overnight at 60 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with saturated NaHCO_3 (aq) and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated to give compound **234** (0.17 g, 91%) as a pale yellow solid. m/z 258
25 $[\text{M}+\text{H}]^+$.

Compound 235: Compound **234** (0.17 g, 0.66 mmol) was dissolved in a 1/1 methanol/THF mixture, 30% sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 50 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH_2PO_4
30 and extracted with EtOAc, then washed with brine, dried with MgSO_4 , and concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in CH_2Cl_2) to give compound **235** (0.12 g, 71%) as a white solid. m/z 258 $[\text{M}+\text{H}]^+$.

Compound TX63559: Compound **235** (0.12 g, 0.47 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C for 1 h, then warmed to room temperature and stirred 1h. Then, pyridine was added, and the reaction mixture was then stirred at
5 60 °C for 5 h. After cooling to room temperature, the reaction mixture was concentrated. The crude residue was purified by column chromatography (silica gel, 50 % EtOAc in CH₂Cl₂) to give **TX63559** (85 mg, 71%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ 8.29 (s, 1H), 7.25 (s, 1H), 3.95 (s, 3H), 3.11 (dd, 1H, *J* = 6.3, 11.3 Hz), 2.67 (dd, 1H, *J* = 6.3, 13.8 Hz), 2.60 (dd, 1H, *J* = 11.4, 13.6 Hz), 1.40 (s, 6H),
10 1.32 (s, 3H); *m/z* 256 [M+H]⁺.

Compound 236: To a solution of **68** (260 mg, 0.70 mmol) in dioxane (4 mL) was added Et₃N (0.5 mL) and CuI (6.7 mg, 0.035 mmol). Nitrogen was bubbled through the mixture for 15 min. TMS-acetylene (207 mg, 2.11 mmol) and (Ph₃P)₂PdCl₂ (14.8 mg, 0.021 mmol) were added, and the mixture was heated in a
15 sealed vessel at 80 °C overnight. The mixture was cooled and concentrated. Flash chromatography (20% EtOAc/DCM) gave 9 mg (3%) of **236** as a white solid. MS (APCI): *m/z* 387.1 [M+H]⁺.

Compound 237: Compound **236** (30 mg, 0.077 mmol) was taken up in THF (3 mL) and 1M HCl (0.5 mL) was added. The solution was stirred for 3 d, then
20 diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were dried over MgSO₄ and concentrated to give 26 mg (98%) of **237** as an oil. MS (APCI): *m/z* 343 [M+H]⁺.

Compound 238: A solution of **237** (26 mg, 0.076 mmol) in ethyl formate (3 mL) was cooled in an ice bath. NaOMe (0.2 g, 30 wt% in MeOH) was added
25 dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was quenched by the addition of sat. aq. KH₂PO₄ (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated to give 26 mg (>100%) of the **238** as an oil. MS (APCI): *m/z* 299 [M+H]⁺.

Compound 239: Compound **238** (0.076 mmol) was taken up in EtOH (3 mL) and water (0.5 mL). Hydroxylamine hydrochloride (5.8 mg, 0.084 mmol) was added
30 and the reaction was heated at 60 °C overnight. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine (10

mL), dried over MgSO_4 , and concentrated to give 27 mg (>100%) of **239** as a tan solid. MS (APCI): m/z 296 $[\text{M}+\text{H}]^+$.

Compound 240: Compound **239** (0.076 mmol) was taken up in THF (3 mL) and MeOH (1 mL) and NaOMe (0.1 g, 30 wt% in MeOH) was added. The solution
5 was heated at 50 °C for 4 h, then allowed to cool to room temperature. Sat. aq. KH_2PO_4 (10 mL) was added, and the mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , and concentrated. Flash chromatography (1:4 EtOAc/DCM) gave 11 mg (50%) of **240** as a white solid. MS (APCI): m/z 296 $[\text{M}+\text{H}]^+$.

Compound TX63651: Compound **240** (11 mg, 0.037 mmol) was taken up
10 in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (6.4 mg, 0.022 mmol) was added and the solution was stirred 3 h at 0 °C. Pyridine (0.05 mL) was added and the solution was heated at 60 °C overnight. After cooling, the solution was concentrated under vacuum to brown oil. Flash chromatography (25%
15 EtOAc/Hexane) gave 6 mg (55%) of **TX63651** as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 8.45 (s, 1H), 3.91 (s, 3H), 3.63 (s, 1H), 2.85-2.78 (dd, 1H, $J = 5.9, 11.5, 5.6$ Hz), 2.61-2.52 (m, 1H), 2.18-2.13 (dd, 1H, $J = 1.9, 10.26, 1.9$), 1.99-1.93 (m, 1H), 1.92-1.80 (m, 1H), 1.48 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H); MS (APCI): m/z 294 $[\text{M}+\text{H}]^+$.

Compound 241: Compound **68** (305 mg, 0.826 mmol) was dissolved in
20 DMAc (5 mL). To this solution was added $\text{Zn}(\text{CN})_2$ (65 mg, 0.56 mmol), dppf (95 mg, 0.17 mmol) and Na_2CO_3 (90 mg, 0.83 mmol). Nitrogen was bubbled through the mixture for 10 min. $\text{Pd}(\text{OAc})_2$ (20 mg, 0.09 mmol) was added and nitrogen was bubbled for 10 min. The suspension was heated to 120 °C for 16 hours. The reaction
25 mixture was quenched with 25 mL of water and extracted with ether (2×50 mL). The organic extracts were concentrated, purified on a silica gel column, eluted with 5–20% EtOAc/Hexanes to give **241** as an off-white solid (0.21 g, 80% yield). MS (APCI): $[\text{M}+\text{H}]^+$ 316.

Compound 242: A solution of **241** (145 mg, 0.46 mmol) in MeOH (5 mL)
30 was treated with 3N $\text{HCl}_{(\text{aq})}$ (1.5 mL), stirred at room temperature overnight. The reaction mixture was concentrated, extracted with EtOAc (2×25 mL) and sat'd $\text{NaHCO}_{3(\text{aq})}$ (15 mL). The organic layer was dried with MgSO_4 , concentrated to give **241** as a foam (120 mg, 96%). MS (APCI): $[\text{M}+\text{H}]^+$ 272.

Compound 243: To a solution of **242** (120 mg, 0.44 mmol) in 5 mL of HCOOEt at RT, 30% NaOMe in MeOH (0.5 g, 6 eq) was added dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat. aq. KH₂PO₄. The mixture was extracted with EtOAc (2×25 mL). The combined
5 organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **243** (130 mg, 100% yield). MS (APCI): [M+H]⁺ 300.

Compound 244: To a solution of **243** (130 mg, 0.44 mmol) in 5 mL of EtOH, NH₂OH·HCl salt (62 mg, 2 eq) was added, and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and
10 extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **244** (130 mg, 100%). MS (APCI): [M+H]⁺ 297.

Compounds 245 and 246: To a solution of **244** (130 mg, 0.44 mmol) in 2 mL of THF and 1 mL of MeOH, 30% NaOMe (0.66 g, 8 eq) was added, and the solution
15 was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with KH₂PO₄ (sat., 15 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give a mixture of **245** and **246** (130 mg, 100% yield). MS (APCI): 297 [M+H]⁺ and 315.

TX63613 and TX63619: To a mixture of **245** and **246** (130 mg, 0.44 mmol)
20 in 2 mL of DMF at 0 °C, DBDMH (72 mg, 0.55 eq) was added, and the solution was stirred for 2 hours. Pyridine (1 g, 30 eq) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 10–100% EtOAc/Hexanes to collect the first less polar
25 dicarbonitrile **TX63613** as an off-white solid (50 mg, 39% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.36 (s, 1H), 3.98 (s, 3H), 2.90 (dd, 1H, J=15, 5 Hz), 2.64 (ddd, 1H, J=15, 10, 5 Hz), 2.12 (d, 1H, J=10 Hz), 1.98 (dd, 1H, J=15, 5 Hz), 1.86 (ddd, 1H, J=25, 15, 5 Hz), 1.45 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H); MS (APCI): [M+H]⁺ 295; followed by the second more polar carboxamide **TX63619** as an off-white solid (10
30 mg, 8% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.46 (s, 1H), 7.45 (s, 1H), 7.26 (s, 1H), 3.93 (s, 3H), 2.85 (dd, 1H, J=15, 5 Hz), 2.62-2.66 (m, 1H), 2.15 (d, 1H, J=10 Hz), 1.89-1.92 (m, 1H), 1.71-1.84 (m, 1H), 1.41 (s, 3H), 1.25 (s, 3H), 1.10 (s, 3H); MS (APCI): [M+H]⁺ 313.

Compound 247: Compound **241** (110 mg, 0.34 mmol) was added to 10 mL MeOH saturated with HCl and the mixture was heated at 60 °C for 16 hours in a sealed bottle. The reaction mixture was concentrated, and quenched with K₂CO₃ (conc., 25 mL), and extracted with EtOAc (2×25mL). The extracts were dried with
5 MgSO₄ and concentrated to give **247** as a white solid (105 mg, 100% yield). MS (APCI): *m/z* [M+H]⁺ 305.

Compound 248: To a solution of **247** (105 mg, 0.36 mmol) in 5 mL of HCOOEt at RT, 30% NaOMe in MeOH (0.2 g, 3eq) was added dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat.
10 aq. KH₂PO₄. The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **247** (110 mg, 88% yield). MS (APCI): *m/z* [M+H]⁺ 347.

Compound 249: To a solution of **248** (110 mg, 0.32 mmol) in 5 mL of EtOH, NH₂OH·HCl salt (50 mg, 2eq) was added, and the solution was heated at 50 °C
15 overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2x25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **249** (110 mg, 100%). MS (APCI): *m/z* [M+H]⁺ 344.

Compound 250 and 251: To a solution of **248** (110 mg, 0.32 mmol) in 2 mL
20 of THF and 1 mL of MeOH, NaOEt (40 mg of Na metal in 1 mL of EtOH, 5 eq) was added, and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with KH₂PO₄ (sat., 15 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give a mixture of **250** and **251** (110 mg, 100% yield). MS
25 (APCI): *m/z* [M+H]⁺ 316 and 344.

Compound TX63630 and TX63631: To a mixture of **250** and **251** (110 mg, 0.32 mmol) in 2 mL of DMF at 0 °C, DBDMH (51 mg, 0.55 eq) was added, and the solution was stirred for 2 hours. Pyridine (1 g, 40 eq) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a
30 silica gel column, eluted with 10–100% EtOAc/Hexanes to give the less polar ethyl ester **TX63630** as an off-white solid (40 mg, 37% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.48 (s, 1H), 4.40-4.34 (q, 2H, J = 7.1, 7.2, 7.1 Hz), 4.15 (s, 3H), 3.10-3.00 (dd, 1H, J = 5.3, 12.32, 5.3 Hz), 2.75-2.63 (m, 1H), 2.18-2.12 (dd, 1H, J = 1.7, 10.49, 1.8), 2.01-1.93 (dd, 1H, J = 6.91, 6.44, 1.93), 1.92-1.81 (m, 1H), 1.48 (s, 3H), 1.44-1.37 (t,

3H, $J = 7.13, 7.08$), 1.31 (s, 3H), 1.25 (s, 3H); MS (APCI): m/z $[M+H]^+$ 342. And the more polar acid **TX63631** was isolated as an off-white solid (13 mg, 13% yield). ^1H NMR (500 MHz, DMSO) δ 13.40 (s, 1H), 8.47 (s, 1H), 4.05 (s, 3H), 2.92 (dd, 1H, $J = 5.6, 11.8, 5.6$ Hz), 2.63-2.54 (m, 1H), 2.19-2.13 (m, 1H), 1.95-1.88 (m, 1H), 1.88-1.75 (m, 1H), 1.42 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H); MS (APCI): m/z $[M+H]^+$ 314.

Compound 252: To a solution of **241** (160 mg, 0.51 mmol) in toluene (5 mL) was added trimethylsilylazide (0.13 mL, 1.01 mmol) followed by dibutyltin oxide (13 mg, 0.051 mmol). The mixture was heated overnight in a 110 °C oil bath. The solution was cooled and transferred to a thick-walled vessel. Additional portions of trimethylsilylazide (0.13 mL) and dibutyltin oxide (13 mg) were added and the solution was heated overnight in a 130 °C oil bath. After cooling, MeOH (5 mL) was added and the solution was concentrated and dried under vacuum to give 0.26 g of crude **252** as an orange solid, MS (APCI): m/z 359.1 $[M+H]^+$.

Compound 253a: Compound **252** was taken up in DMF (5 mL), and potassium carbonate (0.35 g, 2.55 mmol) was added followed by methyl iodide (0.16 mL, 2.55 mmol). The mixture was stirred overnight, water (20 mL) was added and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , concentrated, and dried under vacuum. Flash chromatography (50% EtOAc/Hexane) gave 112 mg (59%) of **253a** as a white solid. MS (APCI): m/z 373.1 $[M+H]^+$.

Compound 254a: Compound **253a** (108 mg, 0.29 mmol) was taken up in THF (4 mL) and 1M HCl (1 mL) was added. The solution was stirred for 3 d, diluted with sat. NaHCO_3 (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO_4 and concentrated to give 95 mg (100%) of **254a** as a white solid. MS (APCI): m/z 329.0 $[M+H]^+$.

Compound 255a: A solution of **254a** (95 mg, 0.29 mmol) in ethyl formate (4 mL) was cooled in an ice bath. NaOMe (0.5g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was quenched by the addition of sat. aq. KH_2PO_4 (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , and concentrated to give 100 mg (97%) of the **254a** as a white solid. MS (APCI): m/z 357.0 $[M+H]^+$.

Compound 256a: Compound **255a** (100 mg, 0.28 mmol) was taken up in EtOH (2 mL), THF (2 mL), and water (0.5 mL). Hydroxylamine hydrochloride (21

mg, 0.31 mmol) was added and the reaction was stirred at room temperature for 30 min, then heated at 50 °C overnight. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (20 mL), dried over
5 MgSO₄, concentrated, and dried under vacuum to give 97 mg (98%) of **256a** as a white solid. MS (APCI): *m/z* 354.0 [M+H]⁺.

Compound 257a: Compound **256a** (97 mg, 0.27 mmol) was taken up in THF (3 mL) and MeOH (1 mL) and NaOMe (0.5 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 4 h, then allowed to cool to room temperature and
10 stirred overnight. Sat. aq. KH₂PO₄ (20 mL) was added, and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography (1:3 EtOAc/DCM) gave 86 mg (89%) of **257a** as a white solid. MS (APCI): *m/z* 354.0 [M+H]⁺.

Compound TX63665: Compound **256a** (86 mg, 0.24 mmol) was taken up in
15 DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (42 mg, 0.15 mmol) was added and the solution was stirred 2 h at 0 °C. Pyridine (0.3 mL) was added and the solution was heated at 60 °C for 5 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (15% EtOAc/DCM) gave 64 mg (74%) of **TX63665** as a white solid.
20 ¹H NMR (500 MHz, CDCl₃) δ 8.53 (s, 1H), 4.46 (s, 3H), 4.24 (s, 3H), 3.15 (dd, 1H, *J* = 6.1, 17.1 Hz), 2.78 (m, 1H), 2.24 (m, 1H), 1.87-2.05 (m, 2H), 1.55 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H); MS (APCI): *m/z* 352.0 [M+H]⁺.

Compound 253b: Compound **252** (0.41 mmol) was taken up in DMF (3 mL), and K₂CO₃ (0.28 g, 2.06 mmol) was added followed by benzyl bromide (0.1 mL, 0.82
25 mmol). The mixture was stirred overnight, water (20 mL) was added and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum. Flash chromatography (30–50% EtOAc/Hexane) gave 47 mg (26%) of **253b** as white foam. MS (APCI): *m/z* 449.3 [M+H]⁺.

30 **Compound 254b:** Compound **253b** (44 mg, 0.098 mmol) was taken up in THF (3 mL) and 1M HCl (0.5 mL) was added. The solution was stirred for 2 d, diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and

concentrated to give 40 mg (100%) of **254b** as a white solid. MS (APCI): m/z 405.3 $[M+H]^+$.

Compound 255b: A solution of **254b** (95 mg, 0.23 mmol) in THF (3 mL) and ethyl formate (1 mL) was cooled in an ice bath. NaOMe (0.4 g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath and quenched by the addition of sat. aq. KH_2PO_4 (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to give 105 mg (>100%) of **255b** as a white foam. MS (APCI): m/z 433.1 $[M+H]^+$.

Compound 256b: Compound **255b** (0.23 mmol) was taken up in EtOH (1 mL), THF (3 mL), and water (0.5 mL). Hydroxylamine hydrochloride (19 mg, 0.28 mmol) was added and the reaction was heated at 50 °C for 4 h, then cooled and concentrated. The residue was diluted with sat. aq. $NaHCO_3$ (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 100 mg (100%) of **256b** as a white solid. MS (APCI): m/z 430.2 $[M+H]^+$.

Compound 257b: Compound **256b** (100 mg, 0.23 mmol) was suspended in 3:1THF/MeOH (4 mL) and NaOMe (0.4 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 4 h, then cooled and concentrated. Sat. 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, dried over $MgSO_4$, concentrated, and dried under vacuum to give 70 mg (70%) of **257b** as white foam. MS (APCI): m/z 430.2 $[M+H]^+$.

Compound TX63729: Compound **257b** (70 mg, 0.16 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (28 mg, 0.098 mmol) was added and the solution was stirred 90 min at 0 °C. Pyridine (0.3 mL) was added and the solution was heated at 60 °C for 3 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (5% EtOAc/DCM) gave 55 mg (79%) of **TX63729** as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.38 (m, 5H), 5.81 (s, 2H), 4.18 (s, 3H), 3.08 (ddd, 1H, $J = 1.6, 6.0, 17.1$ Hz), 2.73 (ddd, 1H, $J = 7.1, 11.7, 18.7$ Hz), 2.18 (dd, 1H, $J = 2.1, 12.1$ Hz), 1.81-1.99 (m, 2H), 1.48 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H); MS (APCI): m/z 428.2 $[M+H]^+$.

Compound 253c: Crude **252** (0.41 mmol) was taken up in DMF (3 mL), and K_2CO_3 (0.28 g, 2.05 mmol) was added followed by isopropyl iodide (0.2 mL, 2.05 mmol). The mixture was stirred overnight, water (20 mL) was added and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed
5 with brine, dried over $MgSO_4$, concentrated, and dried under vacuum to give 0.18 g of impure **253c** as a brown oil. MS (APCI): m/z 401.2 $[M+H]^+$.

Compound 254c: Crude **253c** (0.18 g) was taken up in THF (3 mL) and 1M HCl (0.5 mL) was added. The solution was stirred for 5 d, diluted with sat. $NaHCO_3$ (20 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were
10 washed with brine, dried over $MgSO_4$ and concentrated to give 0.15 g of a crude oil. Flash chromatography (30% EtOAc/Hexane) gave 111 mg (76%) of **254c** as a colorless oil. MS (APCI): m/z 357.2 $[M+H]^+$.

Compound 255c: A solution **254c** (0.11 g, 0.31 mmol) in THF (3 mL) and ethyl formate (1 mL) was cooled in an ice bath. NaOMe (0.5 g, 30 wt% in MeOH)
15 was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath and quenched by the addition of sat. aq. KH_2PO_4 (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 113 mg (95%) of **255c** as a white foam. MS (APCI): m/z 385.1
20 $[M+H]^+$.

Compound 256c: Compound **255c** (113 mg, 0.29 mmol) was taken up in EtOH (1 mL), THF (2 mL), and water (0.5 mL). Hydroxylamine hydrochloride (25 mg, 0.35 mmol) was added and the reaction was heated at 50 °C for 3 h, then cooled and concentrated. The residue was diluted with sat. aq. $NaHCO_3$ (20 mL) and
25 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 111 mg (99%) of **256c** as a white solid. MS (APCI): 382.2 $[M+H]^+$.

Compound 257c: Compound **256c** (111 mg, 0.29 mmol) was suspended in THF:MeOH (4 mL) and NaOMe (0.5 g, 30 wt% in MeOH) was added. The solution
30 was heated at 50 °C for 4 h, then cooled and concentrated. Sat. 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, dried over $MgSO_4$, concentrated, and dried under vacuum to give 112 mg (100%) of **257c** as a light yellow foam. MS (APCI): m/z 382.2 $[M+H]^+$.

Compound TX63734: Compound **257c** (111 mg, 0.29 mmol) was taken up in DMF (3 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (50 mg, 0.17 mmol) was added and the solution was stirred 90 min. at 0 °C. Pyridine (0.5 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, the solution was concentrated and dried under vacuum to give 0.18 g of a light brown solid. Flash chromatography (5% EtOAc/DCM) gave 75 mg (68%) of **TX63734** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 5.16 (septet, 1H, *J* = 6.7 Hz), 4.22 (s, 3H), 3.13 (ddd, 1H, *J* = 1.3, 6.0, 17.1 Hz), 2.77 (ddd, 1H, *J* = 7.1, 11.7, 17.1 Hz), 2.22 (dd, 1H, *J* = 2.2, 12.1 Hz), 1.94 (m, 2H), 1.71 (d, 6H, *J* = 6.7 Hz), 1.52 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H); MS (APCI): *m/z* 380.2 [M+H]⁺.

Compound 258: Compound **241** (115 mg, 0.36 mmol) was suspended in EtOH (2 mL) and hydroxylamine (70 mg, 50% solution in water) was added. Heated at 50 °C overnight, then cooled and concentrated to a white solid to afford **258**. MS (APCI): *m/z* 349.1 [M+H]⁺.

Compound 259: Compound **258** (0.36 mmol) was suspended in dioxane (1 mL) and a solution of dimethylacetamide dimethyacetal (146 mg, 1.09 mmol) in dioxane (1 mL) was added. The mixture was heated at 60 °C for 2 h. The mixture was cooled and concentrated to a yellow solid. Flash chromatography (20% EtOAc/DCM) gave 130 mg (96%) of **259** as a white solid. MS (APCI) 373.1 [M+H]⁺.

Compound 260: Compound **259** (125 mg, 0.34 mmol) was taken up in THF (4 mL) and 1M HCl (1 mL) was added. The solution was stirred for 2 d, diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 110 mg (100%) of **260** as a white solid. MS (APCI): *m/z* 329.1 [M+H]⁺.

Compound 261: A solution of **260** (110 mg, 0.33 mmol) in THF (2 mL) and ethyl formate (2 mL) was cooled in an ice bath. NaOMe (0.6 g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath and quenched by the addition of sat. aq. KH₂PO₄ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated to give 120 mg (100%) of **261** as a white solid. MS (APCI): *m/z* 357.1 [M+H]⁺.

Compound 262: Compound **261** (119 mg, 0.33 mmol) was suspended in EtOH (2 mL), THF (2 mL), and water (0.5 mL). Hydroxylamine hydrochloride (28

mg, 0.40 mmol) was added and the reaction was stirred at room temperature for 30 min, and then heated at 50 °C overnight. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (20 mL), dried
5 over MgSO₄, concentrated. Flash chromatography (15% EtOAc/DCM) gave 90 mg (77%) of **262** as a white solid. MS (APCI): *m/z* 354.1 [M+H]⁺.

Compound 263: Compound **262** (90 mg, 0.25 mmol) was suspended in THF (3 mL) and MeOH (1 mL) and NaOMe (0.5 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 3 h, then allowed to cool to room temperature and
10 concentrated. Sat. aq. KH₂PO₄ (20 mL) was added, and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 88 mg (98%) of **263** as a light yellow solid. MS (APCI): *m/z* 354.1 [M+H]⁺.

Compound TX63723: Compound **263** (88 mg, 0.25 mmol) was taken up in
15 DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (43 mg, 0.15 mmol) was added and the solution was stirred 90 min. at 0 °C. Pyridine (0.4 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (5% EtOAc/DCM) gave 68 mg (78%) of **TX63723** as a light yellow
20 solid. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1H), 4.10 (s, 3H), 3.02 (ddd, 1H, *J* = 1.3, 6.0, 17.3 Hz), 2.64 (m, 1H), 2.59 (s, 3H), 2.12 (dd, 1H, *J* = 2.1, 12.1 Hz), 1.75-1.94 (m, 2H), 1.43 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H); MS (APCI) *m/z* 352.1 [M+H]⁺.

Compound 264: Crude **252** (0.41 mmol) was taken up in pyridine (3 mL), and acetic anhydride (0.42 mL, 4.44 mmol) was added. The solution was heated at
25 110 °C for 3 h, then cooled and concentrated. The residue was diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 0.35 g of a dark brown oil. Flash chromatography (1:1 EtOAc/Hexane) gave 225 mg of impure **264** as a white foam. MS (APCI): *m/z* 373.1
30 [M+H]⁺.

Compound 265: Impure **264** (0.22 g, 0.59 mmol) was taken up in THF (3 mL) and 1M HCl (0.5 mL) was added. The solution was stirred for 2 d, diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 0.20 g of

a crude foam. Flash chromatography (1:1 EtOAc/Hexane) gave 66 mg (34%) of **264** as a white solid. MS (APCI): m/z 329.1 $[M+H]^+$.

Compound 266: A solution of **265** (66 mg, 0.20 mmol) in THF (2 mL) and ethyl formate (2 mL) was cooled in an ice bath. NaOMe (0.36 g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath, quenched by the addition of sat. aq. KH_2PO_4 (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 71 mg (99%) of **266** as a white solid. MS (APCI): m/z 357.2 $[M+H]^+$.

Compound 267: Compound **266** (71 mg, 0.20 mmol) was taken up in EtOH (1 mL), THF (2 mL), and water (0.5 mL). Hydroxylamine hydrochloride (17 mg, 0.24 mmol) was added and the reaction was heated overnight at 50 °C, then cooled and concentrated. The residue was diluted with sat. aq. $NaHCO_3$ (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. Flash chromatography (1:1 EtOAc/DCM) gave 20 mg (28%) of **267** as a white solid. MS (APCI): m/z 354.2 $[M+H]^+$.

Compound 268: Compound **267** (20 mg, 0.057 mmol) was taken up in 1:1 THF/MeOH (2 mL) and NaOMe (0.1 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 6 h, then cooled and concentrated. Sat. aq. KH_2PO_4 (10 mL) was added, and the mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated, and dried under vacuum to give 20 mg (100%) of **268** as a beige foam. MS (APCI): m/z 354.1 $[M+H]^+$.

Compound TX63735: Compound **268** (20 mg, 0.057 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (9.7 mg, 0.034 mmol) was added and the solution was stirred 90 min. at 0 °C. Pyridine (0.1 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, the solution was concentrated and dried under vacuum. Flash chromatography (10% EtOAc/DCM) gave 12 mg (60%) of **TX63735** as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 4.23 (s, 3H), 3.06 (ddd, 1H, J = 1.0, 6.0, 11.2 Hz), 2.75 (ddd, 1H, J = 7.2, 11.7, 17.1 Hz), 2.62 (s, 3H), 2.19 (dd, 1H, J = 2.0, 12.1 Hz), 1.95 (m, 2H), 1.50 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H); MS (APCI): m/z 352.1 $[M+H]^+$.

Compound 269: To a solution of **241** (0.47 g, 1.49 mmol) in EtOH (6 mL) was added water (3 mL) followed by KOH (0.42 g, 7.45 mmol). The solution was stirred at room temperature for 3 d. Sat. KH_2PO_4 solution was added, and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed
5 with brine, dried over MgSO_4 , concentrated, and dried under vacuum to give 0.50 g (100%) of **269** as a white foam. MS (APCI): m/z 334.2 $[\text{M}+\text{H}]^+$.

Compound 270: DMA-dimethylacetal (2 mL) was added to **269** (135 mg, 0.40 mmol) and the mixture was heated at 80 °C for 2 h. The solution was cooled and concentrated to give **270** as a white solid. MS (APCI): m/z 403.3 $[\text{M}+\text{H}]^+$.

10 **Compound 271:** Hydroxylamine hydrochloride (36 mg, 0.52 mmol) was suspended in dioxane (1 mL) and Et_3N (0.073 mL, 0.52 mmol) was added. The mixture was sonicated for several minutes. A solution of **270** (0.40 mmol) in dioxane (2 mL) was added followed by acetic acid (50 mg, 0.83 mmol). The mixture was heated at 80 °C for 1 h, and then additional hydroxylamine hydrochloride (5 mg) was
15 added followed by acetic acid (100 mg). The mixture was heated at 80 °C for 3 h, then allowed to cool to room temperature and stirred overnight. The mixture was diluted with sat. 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 sticky white foam. Flash
20 chromatography (25% EtOAc/Hexane) gave 86 mg (58%) of **271** as a white foam. MS (APCI): m/z 373.2 $[\text{M}+\text{H}]^+$.

Compound 272: Compound **271** (83 mg, 0.22 mmol) was taken up in THF (2 mL) and 1M HCl (0.5 mL) was added. The solution was stirred 2 d, then diluted with sat. NaHCO_3 (10 mL) and extracted with EtOAc (2×25 mL). The combined organic
25 extracts were washed with brine, dried over MgSO_4 , concentrated, and dried under vacuum to give 75 mg (100%) of **272** as a white foam. MS (APCI): m/z 329.1 $[\text{M}+\text{H}]^+$.

Compound 273: Compound **272** (73 mg, 0.22 mmol) was taken up in THF (2 mL) and ethyl formate (1 mL) and cooled in an ice bath. NaOMe (0.4 g, 30 wt% in
30 MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture cooled in an ice bath, quenched by the addition of sat. aq. KH_2PO_4 (10 mL), and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , concentrated, and dried under

vacuum to give 85 mg (>100%) of **273** as a light yellow solid. MS (APCI): m/z 357.1 $[M+H]^+$.

Compound 274: Compound **273** (0.22 mmol) was taken up in THF (2 mL), EtOH (1 mL) and water (0.5 mL). Hydroxylamine hydrochloride (23 mg, 0.33 mmol) was added and the reaction was heated at 50 °C for 3 h. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO_3 (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO_4 , concentrated, and dried under vacuum to give 80 mg (>100%) of **274** as a light yellow foam. MS (APCI): m/z 354.1 $[M+H]^+$.

Compound 275: Compound **274** (Step 5) (0.22 mmol) was taken up in 2:1 THF/MeOH (3 mL) and NaOMe (0.4 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 3 h, then allowed to cool to room temperature and concentrated. Sat. aq. KH_2PO_4 (10 mL) was added, and the mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , and concentrated to give 78 mg of a light yellow foam. Flash chromatography (25% EtOAc/Hexane) gave 60 mg (77%) of **275** as a white foam. MS (APCI): m/z 354.2 $[M+H]^+$.

Compound TX63760: Compound **275** (59 mg, 0.17 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (29 mg, 0.10 mmol) was added and the solution was stirred 90 min at 0 °C. Pyridine (0.3 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (5% EtOAc/DCM) gave 49 mg (84%) of **TX63760** as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.46 (s, 1H), 4.24 (s, 3H), 3.16 (dd, 1H, $J = 5.8, 17.7\text{ Hz}$), 2.80 (ddd, 1H, $J = 7.1, 11.6, 17.5\text{ Hz}$), 2.48 (s, 3H), 2.19 (dd, 1H, $J = 1.7, 12.1\text{ Hz}$), 1.95 (m, 2H), 1.50 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H); MS (APCI): m/z 352.2 $[M+H]^+$.

Compound 276: Compound **269** (29 mg, 0.087 mmol) was slurried in DMF-DMA (2 mL) and heated at 80 °C overnight. The solution was cooled and concentrated to give **276** as a white solid. MS (APCI): m/z 389.1 $[M+H]^+$.

Compound 277: Compound **276** (0.087 mmol) was taken up in dioxane (1 mL) and HOAc (4 drops) was added followed by methyl hydrazine (1 drop). The solution was heated at 80 °C for 2 h, then cooled and concentrated to give the title compound **277** as an off-white solid. MS (APCI): m/z 372.1 $[M+H]^+$.

Compound 278: Compound **277** (0.087 mmol) was taken up in THF (3 mL) and 1M HCl (0.5 mL) was added. The solution was stirred overnight, diluted with sat. NaHCO₃ (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 28 mg (100%) of **278** as a light yellow oil. MS (APCI): m/z 328.1 [M+H]⁺.

Compound 279: Compound **278** (28 mg, 0.087 mmol) in ethyl formate (2 mL) was cooled in an ice bath. NaOMe (0.15 g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was quenched by the addition of sat. aq. KH₂PO₄ (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated to give 30 mg (97%) of **279** as an oil. MS (APCI): m/z 356.0 [M+H]⁺.

Compound 280: Compound **279** (30 mg, 0.084 mmol) was taken up in EtOH (3 mL) and water (0.5 mL). Hydroxylamine hydrochloride (9 mg, 0.13 mmol) was added and the reaction was heated at 60 °C overnight. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, concentrated, and dried under vacuum to give 28 mg (94%) of **280** as a tan foam. MS (APCI): m/z 353.0 [M+H]⁺.

Compound 281: Compound **280** (28 mg, 0.079 mmol) was taken up in 4:1 THF/MeOH (2 mL) and NaOMe (0.15 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 4 h, then allowed to cool to room temperature and stirred overnight. Sat. aq. KH₂PO₄ (10 mL) was added, and the mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography (2–5% MeOH/CHCl₃) gave 22 mg (79%) of **280** as a clear glass. MS (APCI): m/z 353.0 [M+H]⁺.

Compound TX63714: Compound **281** (21 mg, 0.060 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (10.2 mg, 0.15 mmol) was added and the solution was stirred 2 h at 0 °C. Pyridine (0.1 mL) was added and the solution was heated at 60 °C for 6 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (100% EtOAc) gave 15 mg (71%) of **TX63714** as sticky white foam. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 8.04 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.60 (m, 1H), 2.48 (ddd, 1H, *J* = 6.6, 11.4, 16.1 Hz), 2.21 (dd, 1H, *J* = 2.0, 12.0 Hz),

1.78-1.97 (m, 2H), 1.49 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H); MS (APCI): m/z 351.1 $[M+H]^+$.

Compound TX63587: Compound **TX63445** (0.052 g, 0.14 mmol), K_3PO_4 (0.086 g, 0.40 mmol), 4-phenoxyphenylboronic acid (0.047 g, 0.22 mmol) and
5 dimethoxyethane (6 mL) were mixed and the mixture was sparged with N_2 for 3–5 minutes. $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) was added and the reaction was sparged for another 3–5 minutes. The vial was tightly sealed and heated at 80 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 8g) using 3:1 Hexanes/EtOAc to give
10 **TX63587** (25.3 mg) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.38 (dd, 2H, $J = 7.6, 8.1$ Hz), 7.25 (m, 2H), 7.17 (t, 1H, $J = 7.5$ Hz), 7.07 (d, 4H, $J = 7.5$ Hz), 3.83 (s, 3H), 2.65 (dd, 1H, $J = 6.0, 16.1$ Hz), 2.52 (m, 1H), 2.21 (d, 1H, $J = 11.9$ Hz), 1.92 (dd, 1H, $J = 6.6, 13.4$ Hz), 1.83 (dddd, 1H, $J = 6.0, 12.5, 12.8, 12.8$ Hz), 1.55 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H); m/z $[M+H]^+$ 438.0.

Compound TX63588: Compound **TX63445** (0.054 g, 0.146 mmol), K_3PO_4 (0.090 g, 0.42 mmol), 1-methyl-1H-pyrazole-4-boronic acid pinacol ester (0.048 g, 0.23 mmol) and dimethoxyethane (6 mL) were mixed and the mixture was sparged with N_2 for 3–5 minutes. $Pd(PPh_3)_4$ (0.016 g, 0.014 mmol) was added and the reaction was sparged for another for 3–5 minutes. The vial was tightly sealed and heated at 80
20 °C overnight with stirring. The reaction was allowed to cool and was concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 10 g) using 50–100% EtOAc/Hexane to give **TX63588** (11.6 mg) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 3.97 (s, 3H), 3.83 (s, 3H), 2.68 (ddd, 1H, $J = 1.1, 6.0, 15.8$ Hz), 2.52 (dddd, 1H, $J = 6.9, 7.9, 8.0, 11.6$ Hz), 2.17
25 (dd, 1H, $J = 1.9, 12.0$ Hz), 1.92 (dd, 1H, $J = 6.6, 13.5$ Hz), 1.86 (m, 1H), 1.49 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H); m/z $[M+H]^+$ 350.0.

Compound TX63600: Compound **TX63445** (0.049 g, 0.141 mmol), K_3PO_4 (0.091 g, 0.43 mmol), naphthalene-2-boronic acid (0.042 g, 0.28 mmol) and dimethoxyethane (7 mL) were mixed and the mixture was sparged with N_2 for 3–5
30 minutes. $Pd(PPh_3)_4$ (0.014 g, 0.012 mmol) was added and the reaction was sparged for another for 3–5 minutes. Then the vial was tightly sealed and heated at 80 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 10 g) using 3:1 Hexanes/EtOAc to give **TX63600** (23.2 mg) as an off-white solid. ^1H NMR (500

MHz, CDCl₃) δ 8.54 (s, 1H), 7.94 (d, 1H, J=5 Hz), 7.86-7.90 (m, 2H), 7.78 (br s, 1H), 7.54-7.56 (m, 1H), 7.42 (br d, 1H, J=10 Hz), 7.25 (s, 1H), 3.83 (s, 3H), 2.70 (dd, 1H, J=12.5, 5 Hz), 2.56-2.63 (m, 1H), 2.25 (dd, 1H, J=12.5, 2.5 Hz), 1.85-1.95 (m, 2H), 1.55 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H); m/z [M+H]⁺ 396.1.

5 **Compound TX63603:** Compound **TX63445** (0.051 g, 0.146 mmol), K₃PO₄ (0.093 g, 0.44 mmol), naphthalene-1-boronic acid (0.053 g, 0.35 mmol) and dimethoxyethane (7 mL) were mixed and the mixture was sparged with N₂ for 3–5 minutes. Pd(PPh₃)₄ (0.018 g, 0.016 mmol) was added and the reaction was sparged for another for 3–5 minutes. Then the vial was tightly sealed and heated at 80 °C
10 overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 10 g) using 3:1 Hexanes/EtOAc to give **TX63603** (17 mg) as a mixture of interconverting atropisomers as a yellow glass. ¹H NMR (500 MHz, CDCl₃) δ 8.58 (s, 1H), 7.93-7.96 (m, 2H), 7.35-7.56 (m, 5H), 3.59 (s, 1.5H), 3.58 (s, 1.5H), 2.25-2.48 (m, 3H), 1.85-
15 1.88 (m, 2H), 1.61 (s, 1.5H), 1.58 (s, 1.5H), 1.28 (s, 1.5H), 1.27 (s, 1.5H), 1.23 (s, 3H); m/z [M+H]⁺ 396.1.

Compound TX63625: Compound **TX63445** (0.053 g, 0.152 mmol), K₃PO₄ (0.088 g, 0.42 mmol), 3,5-dimethylisoxazole-4-boronic acid (0.042 g, 0.30 mmol) and dimethoxyethane (6 mL) were mixed and nitrogen gas was bubbled through the
20 stirred mixture for 3–5 minutes. Pd(PPh₃)₄ (0.014 g, 0.013 mmol) was added and nitrogen gas was bubbled through the stirred mixture for 3–5 minutes. The vial was tightly sealed and heated at 80 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 8 g) using 3:1 Hexanes/EtOAc followed by preparative thin layer
25 chromatography using 3:1 Hexanes/EtOAc to give **TX63625** (6.6 mg) as a solid. ¹H NMR (500 MHz, CDCl₃) δ 8.51 (s, 1H), 3.63 (s, 3H), 2.49 (m, 1H), 2.43 (m, 1H), 2.36, 2.31 (s, s [1.5, 1.5] 3H), 2.25 (m, 1H), 2.20, 2.15 (s, s [1.5, 1.5] 3H), 2.1 (m, 2H), 1.58 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H); m/z : [M+H]⁺ 365.0.

Compound TX63637: Compound **TX63445** (0.049 g, 0.141 mmol), K₂CO₃
30 (0.061 g, 0.44 mmol), methylboronic acid (0.037 g, 0.64 mmol) and dioxane (8 mL) were mixed and the mixture was sparged with N₂ for 1–2 minutes. Pd(dppf)Cl₂ (0.0167 g, 0.023 mmol) was added and the reaction was sparged for another for 1–2 minutes. The vial was tightly sealed and heated at 90 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was chromatographed

on silica gel (230–400 mesh, 9 g) using 50% Hexanes/EtOAc and rechromatographed on silica gel (230–400 mesh, 4 g) using dichloromethane/methyl-*t*-butyl ether/MeOH, 200/20/1 to give **TX63637** (20 mg) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.48 (s, 1H), 3.76 (s, 3H), 2.65 (dd, 1H, *J* = 5.9, 15.6 Hz), 2.44 (m, 1H), 2.16 (s, 3H), 2.15 (m, 1H), 1.82–1.97 (m, 2H), 1.49 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H); *m/z*: [M+H]⁺ 384.0.

Compound 282: A solution of **241** (175 mg, 0.55 mmol) in THF (5 mL) was cooled in an ice bath. PhMgBr (1.1 mL, 1.0 M in THF, 1.1 mmol) was added, and the solution was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred overnight. Additional PhMgBr (1.1 mL) was added, and after 6 h another portion of PhMgBr (3.3 mL) was added. After stirring overnight, an additional portion of PhMgBr (3.3 mL) was added. After stirring overnight, the solution was cooled in an ice bath and quenched by the slow addition of 1M HCl (5 mL). The mixture was allowed to warm to room temperature and stirred 1 h. 6M HCl (2 mL) was added and the mixture was stirred overnight. Additional THF (5 mL) was added and the mixture was stirred for 3 d. The mixture was concentrated, neutralized with sat. NaHCO₃, and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 0.40 g of an oil. Flash chromatography (30% EtOAc/Hexane) gave 0.21 g of a white foam which was a mixture of **282** and **283** MS (APCI): *m/z* 395, 351 [M+H]⁺.

Compound 283: The mixture of **282** and **283** (0.21 g) was taken up in THF (4 mL) and 1M HCl (1 mL) was added. The solution was stirred overnight, and then heated at 40 °C for 6 h. After cooling, the solution was neutralized with sat. NaHCO₃ (25 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 0.18 g (93%) of **283** as white foam. MS (APCI): *m/z* 351.0 [M+H]⁺.

Compound 284: A solution of **283** (0.18 g, 0.51 mmol) in ethyl formate (3 mL) was cooled in an ice bath. NaOMe (0.9g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath, quenched by the addition of sat. KH₂PO₄ (25 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 184 mg (97%) of **284** as a white solid. MS (APCI): *m/z* 379.0 [M+H]⁺.

Compound 285: Compound **284** (184 mg, 0.49 mmol) was taken up in EtOH (2 mL), THF (5 mL), and water (0.5 mL). Hydroxylamine hydrochloride (37 mg, 0.53 mmol) was added and the reaction was stirred at room temperature for 30 min, and then heated at 50 °C for 4 h. Additional hydroxylamine hydrochloride (10 mg) was added, and heating was continued overnight. The solution was cooled and concentrated. The residue was diluted with sat. NaHCO₃ (20 mL) and 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 180 mg (98%) of **285** as white foam. MS (APCI): *m/z* 376.0 [M+H]⁺.

Compound 286: Compound **285** (180 mg, 0.48 mmol) was taken up in 5:1 THF/MeOH (6 mL) and NaOMe (0.9 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 4 h, then allowed to cool to room temperature and stirred overnight. The solution was concentrated, sat. aq. KH₂PO₄ (25 mL) was added, and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated to give 0.18 g of a light yellow foam. Flash chromatography (40% EtOAc/Hexane) gave 150 mg (83%) of **286** as a white solid. MS (APCI): *m/z* 376.0 [M+H]⁺.

Compound TX63667: Compound **286** (150 mg, 0.40 mmol) was taken up in DMF (3 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (69 mg, 0.24 mmol) was added and the solution was stirred 2 h at 0 °C. Pyridine (0.5 mL) was added and the solution was heated at 55 °C for 5 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (25% EtOAc/Hexane) gave 135 mg (90%) of **TX63667** as white foam. ¹H NMR (500 MHz, CDCl₃) δ 8.52 (s, 1H), 7.76 (m, 2H), 7.66 (m, 1H), 7.54 (m, 2H), 4.06 (s, 3H), 2.24-2.38 (m, 2H), 2.18 (m, 1H), 1.69-1.83 (m, 2H), 1.51 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H); MS (APCI): *m/z* 374.1 [M+H]⁺.

Compound 287: *N*-Chlorosuccinimide (0.124 g, 0.93 mmol) was added to a stirred mixture of **27** (0.235 g, 0.81 mmol) in dichloromethane (10 mL) and the mixture was stirred for 4 days at room temperature. The reaction mixture was concentrated to dryness, and the residue taken up in EtOAc (80 mL), the solution was washed with aqueous NaHCO₃ solution (20 mL), the organic layer was dried MgSO₄, filtered and concentrated to afford **287** (347.8 mg) as a glass/solid. This material was used directly in the next step. *m/z* [M+H]⁺ 325.0, 326.9.

Compound 288: Compound **287** (347.8 mg, 1.07 mmol) was taken up in MeOH, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted with EtOAc (50 mL) and washed with saturated NaHCO₃ (aq), then dried with
5 MgSO₄ and concentrated to give compound **288** (198 mg, 76%), *m/z*: [M+H]⁺ 280.9, 282.8.

Compound 289: Compound **288** (192 mg, 0.68 mmol) was taken up in MeOH, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The residue was extracted
10 with EtOAc (50 mL) and washed with saturated NaHCO₃ (aq), then dried with MgSO₄ and concentrated to give compound **289** (189.8 mg, 91%). *m/z* [M+H]⁺ 308.9.

Compound 290: Compound **289** (189.8 mg, 0.61 mmol) was taken up in ethyl formate, and sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was extracted with
15 EtOAc and washed with KH₂PO₄ (aq), then dried with MgSO₄ and concentrated. The residue was chromatographed on silica gel (230–400 mesh, 12 g) using 3:1 Hexanes/EtOAc to give compound **290** (92.8 mg, 50%) as a white solid. *m/z*: [M+H]⁺ 305.9.

Compound 291: Compound **290** (89 mg, 0.29 mmol) was dissolved in a 3/1
20 MeOH/THF mixture, and sodium methoxide (30 wt% solution in MeOH) was added, and the reaction mixture was stirred at 55 °C for 5 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄ (aq), and the reaction mixture was concentrated. The residue was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude
25 residue was purified by column chromatography (silica gel, 25% EtOAc/Hexanes) to give compound **291** (88.6 mg) as a glass/foam. This material was used directly in the next step.

Compound TX63604: Compound **291** (88.6 mg, 0.29 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. Dibromodimethylhydantoin was
30 added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with

MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc/Hexanes) to give compound **TX63604** (52.5 mg, 60%) as a light yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.39 (s, 1H), 3.77 (s, 3H), 2.65 (dd, 1H, J=17.5, 7.5 Hz), 2.39-2.46 (m, 1H), 2.11 (app d, 1H, J=10 Hz), 1.94 (dd, 1H, J=12.5, 7.5 Hz), 1.82 (ddd, 1H, J=25, 12.5, 5 Hz), 1.45 (s, 3H), 1.24 (s, 3H), 1.21 (s, 3H); *m/z* [M+H]⁺ 303.9.

Compound 292: A solution of **106** (173 mg, 0.57 mmol) in MeOH was treated with 3N HCl solution, stirred at room temperature overnight. The reaction mixture was concentrated, extracted with EtOAc (2×25 mL) and sat. NaHCO₃ solution (15 mL). The organic layer was dried with MgSO₄, concentrated to give **292** which was used directly in the next step.

Compound 293: Compound **292** (assume 0.57 mmol from previous step) was taken up in dioxane (10 mL) and water (6 mL) and cooled to 0 °C. Triethylamine (0.7 mL, 5 mmol), DMAP (0.013 g, 0.11 mmol), and Boc₂O (0.167 g, 0.78 mmol) were added and the reaction mixture was allowed to slowly warm to room temperature. After 3 hours more Boc₂O (0.48 g, 2.2 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to dryness and taken up in MeCN. More catalytic DMAP and Boc₂O (0.21 g, 1.0 mmol) were added and the mixture was warmed to 50 °C. The mixture was concentrated to dryness. EtOAc was added and the insoluble material was removed by filtration. The filtrate was concentrated and resuspended in THF (1 mL). More Boc₂O (0.71 g, 3.3 mmol) was added and the mixture was heated to 55 °C overnight, then heated at 65 °C overnight. The reaction mixture was concentrated to dryness and chromatographed on silica gel (230–400 mesh, 12 g) using 50% EtOAc/Hexane to give the product as a mixture of **293** and bis-Boc products, 0.0471 g. MS: *m/z* [M+H]⁺ 362.1, 462.2.

Compound 294: To a solution of **293** (47.1 mg, ~0.11 mmol) in HCOOEt at RT, 30% NaOMe in MeOH (6 eq) was added dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat. aq. KH₂PO₄. The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **294** (49.8 mg). MS (APCI): [M+H]⁺ 390.1..

Compound 295: To a solution of **294** (0.0498 g, 0.128 mmol) in EtOH, NH₂OH·HCl salt (neutralized with TEA) and pyridinium para-toluenesulfonate solution in MeOH were added, and the mixture was heated at 50 °C for 4 hours. After

concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **295** (91 mg) as a foam (this total reflects combination with an earlier experiment). m/z [M+H]⁺ 387.1.

5 **Compound 296:** To a solution of **295** (0.091 g, 0.23 mmol) in THF and MeOH, 30% NaOMe (8 eq) was added, and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with KH₂PO₄ (sat., 15 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **296** (71 mg, 78%) as an off-white foam. m/z [M+H]⁺ 387.1

10 **Compound TX63594:** Compound **296** (0.071 g, 0.18 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. Dibromodimethylhydantoin was added, and the reaction stirred at 0 °C for 2 hours. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 50% EtOAc/Hexanes) to give compound **TX63594** (8.7 mg, 12.5%). ¹H NMR (500 MHz, d₆-DMSO) δ 8.42 (s, 1H), 5.76 (s, 1H), 3.58 (s, 3H), 3.52-3.55 (m, 1H), 2.31-2.36 (m, 1H), 2.11-2.13 (m, 1H), 1.75-1.86 (m, 2H), 1.45 (s, 9H), 1.39 (s, 3H), 1.21 (s, 3H), 1.12 (s, 3H); m/z [M+H]⁺ 385.1.

20 **Compound TX63642:** Compound **TX63467** (0.021 g, 0.082 mmol) was taken up in a mixture of saturated aqueous NaHCO₃ (0.5 mL) and THF (2.0 mL) and was cooled in an ice bath. A solution of benzoyl chloride in THF was added and the reaction mixture was stirred at 0 °C for a few minutes, after which more benzoyl chloride solution was added and the reaction mixture was stirred for a few more minutes. The reaction mixture was partitioned between EtOAc (40 mL) and brine (2 mL), the layers were separated, the organic layer was dried over MgSO₄, filtered and concentrated to an oil. The oil was chromatographed on silica gel (230–400 mesh, 8 g) using 10:1 Hexanes/EtOAc. Compound **TX63642** (14 mg) was obtained as a clear glass. ¹H NMR (500 MHz, CDCl₃) δ 8.44 (s, 1H), 8.12-8.15 (m, 3H), 7.68 (m, 1H), 7.57 (m, 2H), 2.96 (dd, 1H, *J* = 5.9, 16.7 Hz), 2.69 (m, 1H), 2.24 (dd, 1H, *J* = 2.0, 12.0 Hz), 1.89-2.03 (m, 2H), 1.55 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); m/z [M+H]⁺ 360.0, 255.9 (M-PhCO).

Compound TX63611: TX63579 (17 mg, 0.051 mmol) was taken up in a mixture of saturated NaHCO_3 (aq, 0.5 mL) and THF (1.5 mL), and the mixture was cooled to 0 °C. Acetyl chloride (1 drop, excess) was added, and the reaction mixture was stirred 40 min at 0 °C. Then more acetyl chloride (2 drops, excess) was added, and the reaction mixture was stirred an additional 20 minutes. The reaction mixture was extracted with ethyl acetate (40 mL) and washed with NaCl (aq, 10 mL), then dried with MgSO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 25% EtOAc in Hexanes) to give **TX63611** (2.9 mg, 15%) as a clear glass. ^1H NMR (500 MHz, CDCl_3) δ 8.50 (s, 1H), 7.40-7.46 (m, 3H), 7.26-7.30 (m, 2H), 2.82 (s, 3H), 2.64-2.73 (m, 1H), 2.46-2.55 (m, 1H), 2.30-2.34 (m, 1H), 1.82-1.95 (m, 2H), 1.56 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H); m/z 298 $[\text{M}+\text{H}]^+$.

Compound 297: A solution of **25** (1.4 g, 5.5 mmol) in THF (10 mL) was added to a refluxing mixture of dimethyl carbonate (6 equiv.) and NaH (excess) in THF (10 mL). The reaction was stirred at reflux for 3 h. The reaction mixture was cooled to room temperature, quenched with KH_2PO_4 (aq) and extracted with EtOAc. The organic layer was washed with brine, dried with MgSO_4 and concentrated to give compound **297** (1.5 g, 87%) as a solid. m/z 311 $[\text{M}+\text{H}]^+$.

Compound 298: A mixture of **297** (1 g, 3.17 mmol), methyl hydrazine (300 mg, 6.5 mmol), and EtOH (15 mL) was heated at 60 °C for 16 h. The EtOH was removed, and the crude product was treated with 20 mL of diethyl ether. The precipitate was collected by filtration to give **298** as a white solid (450 mg, 46% yield). MS: m/z $[\text{M}+\text{H}]^+$ 307.

Compound 299: A solution of **298** (190 mg, 1.2 mmol) in MeOH (5 mL) was treated with 3N $\text{HCl}_{(\text{aq})}$ (2 mL), and stirred at RT overnight. The reaction mixture was concentrated, extracted by EtOAc (2×25 mL) and washed with sat'd $\text{NaHCO}_{3(\text{aq})}$ (20 mL). The organic layer was dried with MgSO_4 , and concentrated to give **299** (165 mg, 100% yield). MS: m/z $[\text{M}+\text{H}]^+$ 263.

Compound 300: To a solution of **299** (165 mg, 0.62 mmol) in 5 mL of HCOOEt at RT was added 30% NaOMe in MeOH (1.3 g, 10 eq) dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with KH_2PO_4 . The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , and concentrated in vacuo to give **300** (180 mg, 100% yield). MS: m/z $[\text{M}+\text{H}]^+$ 291.

Compound 301: To a solution of **300** (180 mg, 0.62 mmol) in 10 mL of EtOH was added NH₂OH-HCl (95 mg, 2eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with
5 MgSO₄, and concentrated in vacuo to give **301** as a solid (178 mg, 100% yield). MS: m/z [M+H]⁺ 288.

Compound 302: To a solution of **301** (178 mg, 0.62 mmol) in 2:1 THF/MeOH (3 mL) was added 30% NaOMe (1.2 g, 10eq) dropwise, and the solution was heated at 50 °C for 9 hours. After concentration in vacuo, the residue was mixed
10 with sat. KH₂PO₄ (25 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with water and brine, dried with MgSO₄, concentrated to give **302** as an off-white solid product (175 mg, 99% yield). MS: m/z [M+H]⁺ 288.

Compound TX63676: To a solution of **302** (175 mg, 0.61 mmol) in 2 mL of DMF at 0 °C was added dibromodimethylhydantoin (100 mg, 0.55 eq), and the
15 solution was stirred for 2 hours. Pyridine (1 g) was added and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 20–55% EtOAc/Hexanes to collect a mixture of starting cyanoketone and cyanoenone product (35 mg). This mixture (30 mg) was mixed with DDQ (30 mg, 0.13 mmol) in 1 mL of benzene, and heated to reflux for 16 h. The
20 resulting mixture was dissolved in 10 mL of EtOAc and washed with sat. NaHCO₃ (2×15 mL). The organic layer was concentrated and the residue was purified on a silica gel column, eluted with 20–55% EtOAc/Hexanes to give **TX63676** as an off-white solid (15 mg, 9% yield). ¹H NMR (500 MHz, DMSO) δ 8.46 (s, 1H), 6.47 (s, 1H), 3.19 (s, 3H), 2.09 (m, 1H), 1.95 (m, 2H), 1.66 (m, 1H), 1.52 (s, 3H), 1.39 (m,
25 1H), 1.18 (s, 3H), 1.19 (s, 3H); MS: m/z [M+H]⁺ 286.

Compound 303a-b: To a mixture **298** (670 mg, 2.18 mmol) and K₂CO₃ (910 mg, 6.55 mmol) in 15 mL of DMF at RT was added MeI (625 mg, 4.4 mmol). The mixture was stirred for 16 hours. The reaction mixture was quenched with 100 mL of water and extracted with EtOAc (2×50 mL). After concentration in vacuo, the residue
30 was purified on a silica gel column, eluted with 10–35% EtOAc/Hexanes to give the mixture of **303a-b** (450 mg). MS: m/z [M+H]⁺ 321.

Compound 304a-b: A solution of **303a-b** (450 mg, 1.4 mmol) in MeOH (10 mL) was treated with 3N HCl solution (4 mL), and stirred at RT overnight. The reaction mixture was concentrated, extracted by EtOAc (2×25 mL) and washed with

sat'd NaHCO₃ solution (20 mL). The organic layer was dried with MgSO₄, and concentrated to give a mixture of **304a-b** as an oil (390 mg, 100% yield). MS: m/z [M+H]⁺ 277.

Compound 305a-b: To a solution of **304a-b** (390 mg, 1.4 mmol) in 6 mL of HCOOEt at RT, was added 30% NaOMe in MeOH (1.5 g, 6 eq) dropwise. The reaction mixture was stirred at RT overnight, then poured into water and acidified with KH₂PO₄. The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give a mixture of **305a-b** (425 mg, 100% yield). MS: m/z [M+H]⁺ 305.

Compound 306a-b: To a solution of **305a-b** (425 mg, 1.4 mmol) in 10 mL of EtOH, was added NH₂OH·HCl salt (195 mg, 2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give a mixture of **306a-b** as oil (425 mg, 100% yield). MS: m/z [M+H]⁺ 302.

Compound 307a-b: To a solution of **306a-b** (425 mg, 1.4 mmol) in 1:1 THF/MeOH (4 mL), was added 30% NaOMe (2 g, 8 eq). The solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with sat. KH₂PO₄ (25 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with water and brine, dried with MgSO₄, concentrated to give a mixture of the **307a-b** as oil (425 mg, 100% yield). MS: m/z [M+H]⁺ 302.

Compounds TX63691 and TX63692: To a solution of **307a-b** (425 mg, 1.4 mmol) in 3 mL of DMF at 0 °C was added dibromodimethylhydantoin (222 mg, 0.55 eq), and the solution was stirred for 2 hours. Pyridine (2 g) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 10–50% EtOAc/Hexanes to give **TX63691** as an off-white solid. R_f = 0.5 (Hexane/EtOAc 1:3) (25 mg, 6% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 3.94 (s, 3H), 3.58 (s, 3H), 2.84 (ddd, 1H, J = 1.4, 5.9, 15.2 Hz), 2.59 (m, 1H), 2.11 (dd, 1H, J = 2.4, 11.7 Hz), 1.75–1.91 (m, 2H), 1.45 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H); MS: m/z [M+H]⁺ 300. Continued elution gave a yellow foam, R_f = 0.25 (Hexane/EtOAc 1:3) (260 mg, 62% yield), MS: m/z [M+H]⁺ 302. This material (260 mg) was mixed with DDQ (200 mg, 0.88 mmol) in 10 mL of benzene, and heated to reflux for 16 h. The resulting mixture was dissolved in 25 mL of EtOAc and washed with sat. NaHCO₃ (2×25 mL). The organic layer was

concentrated, and the residue was purified on a silica gel column, eluted with 20–60% EtOAc/Hexanes to give **TX63692** (60 mg, 15% yield) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 3.30 (s, 3H), 2.09 (m, 1H), 1.73–1.92 (m, 3H), 1.48 (s, 3H), 1.42 (m, 1H), 1.42 (s, 3H), 1.21 (s, 6H); MS: *m/z* [M+H]⁺ 300.

5 **Compound 308 and TX63804:** A mixture of **70** (0.48 g, 1.49 mmol) and IBX (1.67 g, 4 eq) in DMF (8 mL) was heated to 65 °C for 6 h. The reaction mixture was quenched with sat. NaHCO₃ solution (25 mL), and extracted with EtOAc (2x50 mL). The combined organic extracts were washed with brine, and dried with MgSO₄. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–
10 35% EtOAc/Hexanes to give the title compound as an off-white solid, **308**, R_f = 0.45 (Hexane/EtOAc 3:2) (286 mg, 60% yield), MS: *m/z* [M+H]⁺ 321. **TX63804** was also isolated as a yellow foam R_f = 0.35 (Hexane/EtOAc 3:2) (15 mg, 3% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, 1H, *J* = 10.4 Hz), 7.39–7.51 (m, 5H), δ 6.08 (d, 1H, *J* = 9.2 Hz), 3.75 (s, 3H), 2.63–2.75 (m, 2H), δ 2.54 (q, 1H, *J* = 13.2 Hz), 1.53 (s, 3H),
15 1.20 (s, 6H); MS: *m/z* [M+H]⁺ 335.

Compound 309: To a solution of **308** (286 mg, 0.89 mmol) in THF (5 mL) and pyridine (0.22 g, 3 eq) was added iodine (0.46 g, 2 eq), and the solution was heated at 60 °C for 16 h. The reaction mixture was quenched with sat. sodium thiosulfate solution (25 mL), and extracted with EtOAc (2x30 mL). The combined
20 organic extracts were washed with brine and dried with MgSO₄. After concentration in vacuo, **309** was isolated as a light colored solid (395 mg, 100%), MS: *m/z* [M+H]⁺ 447.

Compound TX63803: A mixture of **309** (0.2 g, 0.45 mmol) and CuI (0.22g, 2.5 eq) in DMF (5 mL) was heated to 70 °C. FSO₂CF₂CO₂Me (1.3 g, 15 eq) and
25 HMPA (1.4 g, 17 eq) were added sequentially, and the mixture was heated at 70 °C for 6 h. The reaction mixture was quenched with sat. NH₄Cl (25 mL) and extracted with EtOAc (2x25 mL). The combined organic extracts were washed with brine and dried with MgSO₄. After concentration in vacuo, silica gel chromatography, eluted with 5–35% EtOAc/Hexanes, gave **TX63803** as a white solid (110 mg, 63%). ¹H
30 NMR (400 MHz, CDCl₃) δ 8.31 (s, 1H), 7.47 (m, 2H), 7.41 (m, 1H), 7.32 (m, 2H), 3.80 (s, 3H), 2.66 (dd, 1H, *J* = 5.9, 16.1 Hz), 2.54 (ddd, 1H, *J* = 6.6, 11.2, 15.9 Hz), 2.21 (d, 1H, *J* = 11.7 Hz), 1.86 (m, 2H), 1.51 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); MS: *m/z* [M+H]⁺ 389.

Compound 310a-b: Compound **26** (0.72 g, 2.57 mmol), 3-aminopyrazole (0.222 g, 2.67 mmol), *p*-toluenesulfonic acid hydrate (0.025 g, 0.12 mmol) and toluene (70 mL) were heated to reflux with removal of water employing a Dean-Stark trap. The reaction mixture was refluxed overnight and was cooled and concentrated to dryness. The residue was taken up in EtOAc (80 mL), washed with saturated aqueous NaHCO₃ solution (15 mL), and brine (15 mL), dried over MgSO₄, filtered and concentrated to a yellow solid. The solid was chromatographed on silica gel (230–400 mesh, 16 g) using 3:1 Hexanes/EtOAc. The product(s) was/were obtained as follows:

310a (410 mg, 49%) - pure nonpolar isomer as a white solid. m/z [M+H]⁺ 328.0. **310b** (56 mg, 6.7%) - pure polar isomer as a yellow glass, MS: m/z [M+H]⁺ 328.0.

Compound 311a: Compound **311a** (0.326 g, 1.15 mmol) was taken up in MeOH, and 1 N HCl (aq) was added. The mixture was stirred overnight at room temperature. The reaction mixture was then concentrated. The reaction mixture was extracted with EtOAc (50 mL) and washed with saturated NaHCO₃, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography to give compound **311a** (303.5 mg, 100%). m/z [M+H]⁺ 283.9.

Compound 312a: Compound **311a** (0.326 g, 1.15 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH₂PO₄ (aq) and extracted with EtOAc, then dried with MgSO₄ and concentrated to give compound **311a** (393 mg). m/z [M+H]⁺ 312.0.

Compound 313a: A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **312a** (0.393 g, 1.26 mmol). A 9:1 mixture of EtOH/H₂O was added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, then dried with MgSO₄ and concentrated to give compound **313a** (352 mg) as a light yellow solid. m/z [M+H]⁺ 309.0.

Compound 314a: Compound **313a** (0.3518 g, 1.14 mmol) was dissolved in a 3:1 MeOH/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The reaction mixture was stirred at 55 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄, and the reaction mixture was concentrated. The residue was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue

was purified by column chromatography (silica gel, 50% EtOAc/Hexanes) to **313a** (351 mg) as a yellow solid. This material was used directly in the next step.

Compound TX63627 and TX63615: Compound **314a** (0.204 g, 0.66 mmol) was dissolved in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (230–400 mesh, 18 g) using 50% Hexanes/EtOAc to give **TX63627** (34.1 mg, 17%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 9.62 (s, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 7.28 (s, 1H) 3.06 (m, 1H), 2.99 (m, 1H), 2.38 (d, 1H, J = 11.4 Hz), 2.12 (dd, 1H, 6.2, 5.9 Hz), 1.92 (m, 1H), 1.84 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H). *m/z*: [M+H]⁺ 306.9. **TX63615** (59.6 mg, 24%) was also isolated as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 9.58 (s, 1H), 8.38 (s, 1H), 8.11 (s, 1H), 3.04 (dd, 1H, J=20, 5 Hz), 2.90-2.97 (m, 1H), 2.33 (d, 1H, J=10 Hz), 2.08 (dd, 1H, J=15, 5 Hz), 1.83-1.92 (m, 1H), 1.80 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); *m/z* [M+H]⁺ 384.9, 386.8.

Compound TX63626: Compound **TX63615** (0.0486 g, 0.126 mmol), K₃PO₄ (0.086 g, 0.41 mmol), phenylboronic acid (0.024 g, 0.20 mmol) and dimethoxyethane (6 mL) were mixed and nitrogen gas was bubbled through the stirred mixture for 1–2 minutes. Pd(PPh₃)₄ (0.015 g, 0.012 mmol) was added and nitrogen gas was bubbled through the stirred mixture for 1–2 minutes. The vial was tightly sealed and heated at 90 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 9.7 g) using 50% Hexanes/EtOAc, followed by a second purification on silica gel using 3:1 Hexanes/EtOAc to give **TX63626** (12.8 mg, 26%) as a yellowish solid. ¹H NMR (500 MHz, CDCl₃) δ 9.75 (s, 1H), 8.41 (d, 2H, J = 13.3 HZ), 8.03 (d, 2H, J = 7.5 Hz), 7.50 (t, 1H, J = 7.6, 7.6 Hz), 7.33 (t, 1H, J = 7.2, 7.6 Hz), 3.07 (m, 1H), 2.98 (m, 1H), 2.30 (d, 1H, J = 12.4 Hz), 2.11 (m, 1H), 1.95 (m, 1H), 1.89 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H); *m/z*: [M+H]⁺ 383.0.

Compound 311b: Compound **310b** (0.0523 g, 0.16 mmol) was taken up in MeOH, and 1 N HCl (aq) was added. The mixture was stirred overnight at room

temperature. The reaction mixture was then concentrated. The reaction mixture was extracted with EtOAc (50 mL) and washed with saturated NaHCO₃, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography to give compound **311b** (40.7 mg, 90%). m/z [M+H]⁺ 283.9.

5 **Compound 312b:** Compound **311b** (0.0407 g, 0.144 mmol) was taken up in ethyl formate, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with KH₂PO₄ (aq) and extracted with EtOAc, then dried with MgSO₄ and concentrated to give compound **312b** (42.2 mg). m/z [M+H]⁺ 312.0.

10 **Compound 313b:** A solution of 0.1 N hydroxylamine hydrochloride (aq) was added to compound **312b** (0.0422 g, 0.136 mmol). A 9:1 mixture of EtOH/H₂O was added, and the reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was taken up in EtOAc, then dried with MgSO₄ and concentrated to give compound **313b**
15 (43.7 mg) as a yellow glass. m/z [M+H]⁺ 309.0.

Compound 314b: Compound **313b** (0.0437 g, 0.14 mmol) was dissolved in a 3:1 MeOH/THF mixture, and 30% sodium methoxide (30 wt% solution in MeOH) was added. The reaction mixture was stirred at 55 °C for 6 h and then stirred at room temperature overnight. The reaction was quenched by addition of saturated KH₂PO₄,
20 and the reaction mixture was concentrated. The residue was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (silica gel, 50% EtOAc/Hexanes) to give compound **314b** (44.5 mg). This material was used directly in the next step.

Compound TX63617: Compound **314b** (0.0445 g, 0.14 mmol) was dissolved
25 in dry DMF, and the solution was cooled to 0 °C. 1,3-Dibromo-5,5-dimethylhydantoin was added, and the reaction stirred at 0 °C until the starting material was consumed (approximately 30 min), as reported by thin layer chromatography. Then, pyridine was added, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred at 50 °C overnight. After
30 cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with brine, then dried with MgSO₄ and concentrated. The crude residue was purified by column chromatography (230–400 mesh, 10 g) using 50% Hexanes/EtOAc, followed by a second purification on silica gel (230–400 mesh, 8 g) using 1% methyl-*t*-butylether/DCM to give **TX63617** (18 mg, 33%) as a white solid.

^1H NMR (500 MHz, CDCl_3) δ 8.96 (s, 1H), 8.46 (s, 1H), 8.07 (s, 1H), 3.14 (dd, 1H, $J=16.4, 6.0$ Hz), 2.96-3.03 (m, 1H), 2.27 (dd, 1H, $J=11.9, 3.4$ Hz), 2.00-2.11 (m, 2H), 1.51 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H); m/z : $[\text{M}+\text{H}]^+$ 384.9, 386.9.

Compound 316a-b: A solution of a sl. impure mixture of **130**, **315** and an impurity **X** (1.96 g, assume 5.21 mmol, with **130** as the majority fraction) and 3N HCl (20 mL, 60 mmol) in 20 mL of MeOH was stirred at room temperature under N_2 for 16 h. The sample was concentrated, cooled, basified with concentrated NH_4OH to a pH ~ 10 then extracted with CHCl_3 . The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give 1.47 g (91%) of an inseparable mixture of **316a-b** and **X** as light yellow foamy solid, which was used without purification.

Compound 317a-b and X: To a stirring solution of a sl. impure mixture of **316a-b** and **X** (1.47 g, assume 4.73 mmol) and ethyl formate (3.8 mL, 47.0 mmol) in 20 mL of benzene was added dropwise NaOMe, 30 wt.% solution in MeOH (4.4 mL, 23.4 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give 1.51 g (94%) of an inseparable mixture of **317a-b** and **X** as an orange solid, which was used without purification. MS (APCI): m/z 387 (78%) $[\text{M}+\text{H}]^+$ and 339/341 (91/100%) $[\text{M}+\text{H}]^+$.

Compound 318a-b and X: A solution of a sl. impure mixture of **317a-b** and **X** (1.51 g, assume 4.46 mmol) and hydroxylamine hydrochloride (0.47 g, 6.76 mmol) in 20 mL of ethanol was heated at 50 $^\circ\text{C}$ under N_2 for 16 h. The sample was cooled, concentrated and partitioned between EtOAc and sat. NaHCO_3 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give 1.47 g (98%) of an inseparable mixture of **318a-b** and **X** as dark brown foamy solid, which was used without purification. MS (APCI) m/z 384 (79%) $[\text{M}+\text{H}]^+$ and 336/338 (90/100%).

Compound 319a-b and X: To a stirring solution of a sl. impure mixture of **318a-b** and **X** (1.47 g assume 4.37 mmol) at room temperature under N_2 in 50 mL of MeOH was added dropwise NaOMe, 30 wt.% solution in MeOH (4.1 mL, 21.8 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated. The

sample was chromatographed (silica gel, 50% EtOAc/Hexanes) to give 0.81 g (55%) of an inseparable mixture of **319a-b** and **X** as light yellow foamy solid. MS (APCI) m/z 336/338 (96/100%) $[M+H]^+$.

Compound TX63606 and TX63649: To a stirring solution at 0 °C under N₂ of a mixture of **319a-b** and **X** (0.81 g, 2.40 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.38 g, 1.33 mmol). After stirring at 0 °C for 1 h, pyridine (1.90 mL, 23.49 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 16 h. The sample was concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. KH₂PO₄ and sat. NaCl solutions, dried (MgSO₄), filtered and concentrated. The sample was chromatographed (silica gel, 50% EtOAc/Hexanes) to give 0.56 g (69%) of **TX63606** as yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.36 (s, 1H), 3.82 (s, 3H), 2.49-2.60 (m, 2H), 2.38-2.45 (m, 1H), 2.00-2.06 (m, 2H), 1.66-1.75 (m, 1H), 1.39 (s, 3H), 1.28 (br d, 3H, J=5 Hz); MS (APCI) m/z 334/336 (95/100%) $[M+H]^+$. All impure fractions from the above chromatography were combined, concentrated and rechromatographed (silica gel, 25% EtOAc/Hexanes) to give 0.019 g (2%) of **TX63649** as white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 4.00 (s, 3H), 2.51-2.63 (m, 2H), 2.38 (m, 1H), 2.14 (m, 1H), 2.05 (m, 1H), 1.62 (m, 1H), 1.47 (s, 3H), 1.32 (d, 3H, J = 6.8 Hz); MS (APCI) m/z 334/336 (96/100%) $[M+H]^+$.

Compound TX63650 and TX63656: Compound **TX63606** (0.102 g, 0.31 mmol), K₃PO₄ (0.190 g, 0.90 mmol), 3-methylphenylboronic acid (0.065 g, 0.48 mmol) and dimethoxyethane (7 mL) were mixed and the solution was sparged with N₂ for 3–5 min. Pd(PPh₃)₄ (0.022 g, 0.019 mmol) was added and the solution was sparged again for 3–5 minutes. The vial was tightly sealed and heated at 80 °C overnight with stirring. The reaction was allowed cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 10 g) using 3:1 Hexanes/EtOAc to give **TX63650** (52 mg) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 1H), 7.34 (t, 1H, J = 7.6, 7.3 Hz), 7.22 (d, 1H, 7.7 Hz), 7.11 (d, 2H, 7.8 Hz), 3.77 (s, 3H), 2.53 (m, 3H), 2.39 (s, 3H), 2.10 (m, 2H), 1.70 (m, 1H), 1.45 (s, 3H), 1.28 (d, 3H, J = 6.8 Hz); m/z : $[M+H]^+$ 346.1. **TX63656** (2.9 mg) was also isolated as a yellow glass; m/z $[M+H]^+$ 344.0.

Compound TX63659 and TX63663: Compound **TX63606** (0.141 g, 0.42 mmol), K₃PO₄ (0.27 g, 1.27 mmol), 3-fluorophenylboronic acid (0.091 g, 0.65 mmol)

and dimethoxyethane (10 mL) were mixed and the solution was sparged with N₂ for 3–5 min. Pd(PPh₃)₄ (0.027 g, 0.023 mmol) was added and the solution was sparged again for 3–5 minutes. The vial was tightly sealed and heated at 80 °C overnight with stirring. The reaction was cooled, and the solvent was decanted from the solids. The liquid was concentrated to a residue that was chromatographed on silica gel (230–400 mesh, 14 g) using 3:1 Hexanes/EtOAc to give **TX63659** (42 mg) as a yellow foam/glass. ¹H NMR (500 MHz, CDCl₃) δ 8.51 (s, 1H), 7.47 (m, 1H), 7.14 (m, 2H), 7.06 (m, 1H), 3.83 (s, 3H), 2.58 (m, 3H), 2.15 (m, 1H), 2.07 (m, 1H), 1.75 (m, 1H), 1.50 (s, 3H), 1.33 (d, 3H); *m/z*: [M+H]⁺ 350.0; and **TX63663** (6.4 mg) as a yellow glass. ¹H NMR (500 MHz, CDCl₃) δ 8.32 (s, 1H), 7.48 (dd, 1H, *J* = 6.3, 7.79, 7.74), 7.15 (t, 1H, *J* = 8.49, 8.49), 7.12 (d, 1H, *J* = 7.67), 7.06–7.02 (m, 1H), 3.85 (s, 3H), 3.16–3.08 (m, 1H), 2.83–2.75 (m, 1H), 2.68–2.55 (m, 2H), 2.08 (s, 3H), 1.72 (s, 3H); *m/z* [M+H]⁺ 348.0.

Compound TX63664: Compound **TX63606** (0.1209 g, 0.36 mmol), K₃PO₄ (0.227 g, 1.07 mmol), 3-methoxyphenylboronic acid (0.083 g, 0.55 mmol) and dimethoxyethane (8 mL) were mixed and the solution was sparged with N₂ for 3–5 min. Pd(PPh₃)₄ (0.030 g, 0.026 mmol) was added and the solution was sparged again for 3–5 minutes. The vial was tightly sealed and heated at 80 °C overnight with stirring. The reaction cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 15 g) using 3:1 Hexanes/EtOAc to give **TX63664** (34 mg) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 8.52 (s, 1H), 7.42 (t, 1H, *J* = 7.83, 8.06), 6.96 (d, 1H, *J* = 8.38), 6.92 (d, 1H, *J* = 7.58), 6.87 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 2.67 (dd, 1H, *J* = 6.46, 9.77, 6.59 Hz), 2.62–2.54 (m, 2H), 2.16 (t, 1H, *J* = 12.86, 12.75), 2.08–2.00 (m, 1H), 1.80–1.62 (m, 1H), 1.50 (s, 3H), 1.32 (d, 3H, *J* = 6.74); *m/z*: [M+H]⁺ 362.1.

Compound 320a: Compound **130** (0.450 g, 1.27 mmol), K₃PO₄ (0.86 g, 4.05 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (0.554 g, 2.65 mmol) and dimethoxyethane (20 mL) were mixed and the mixture was sparged with N₂ for 3–5 min. Pd(PPh₃)₄ (0.122 g, 0.11 mmol) was added and the reaction was sparged again for 3–5 minutes. The vial was tightly sealed and heated at 95 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was partitioned between EtOAc (100 mL) and saturated aqueous NaCl solution (40 mL), and the organic layer dried over MgSO₄, filtered and concentrated. The resulting oil

was chromatographed on silica gel (230–400 mesh, 18 g) using EtOAc as eluant to give **320a** (374.5 mg) as a yellow foam/glass, m/z $[M+H]^+$ 357.1.

Compound 321a: Compound **320a** (0.371 g, 1.04 mmol) was taken up in MeOH (15 mL) and 1N HCl (5 mL), and the mixture was stirred 3 days at room temperature. The reaction mixture was concentrated to remove MeOH and then partitioned between EtOAc (80 mL) and saturated aqueous NaHCO₃ (15 mL). The organic layer was dried over MgSO₄, filtered and concentrated to an off-white solid (**321a**, 285 mg). m/z : $[M+H]^+$ 313.1.

Compound 322a: Compound **321a** (0.285 g, 0.91 mmol) was taken up in ethyl formate (30 mL) and 30% NaOMe in MeOH (1.1 mL, 5.9 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was partitioned between saturated aqueous KH₂PO₄ (20 mL) and EtOAc (100 mL). The organic layer was dried over MgSO₄, filtered and concentrated to a glass (**322a**, 323 mg). m/z : $[M+H]^+$ 341.0.

Compound 323a: A solution of hydroxylamine hydrochloride (0.105 g, 1.52 mmol) was added to **322a** (0.323 g, 0.95 mmol) in 10:1 EtOH/H₂O (22 mL). The mixture was heated briefly to 50 °C and was then stirred overnight at room temperature. The reaction mixture was concentrated to dryness, partitioned between EtOAc (100 mL) and brine (20 mL) and the organic solution was dried over MgSO₄, filtered and concentrated to a foam/solid (**323a**, 289 mg). m/z : $[M+H]^+$ 338.0.

Compound 324a: Compound **323a** (0.289 g, 0.86 mmol) was taken up in 1:1 MeOH/THF, (20 mL) and 30% NaOMe in MeOH (1.0 mL, 5.4 mmol) was added and the mixture was stirred overnight at room temperature. The reaction was partitioned between saturated KH₂PO₄ (20 mL) and EtOAc (100 mL), the layers were separated and the aqueous layer was back-extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated to give **324a** (275 mg) as a glass/foam. m/z : $[M+H]^+$ 338.0.

Compound TX63690: Compound **324a** (0.275 g, 0.82 mmol) was taken up in benzene (30 mL) and DDQ (0.220 g, 0.969 mmol) was added and the reaction mixture was briefly warmed to 45 °C and a dark precipitate formed. DCM (20 mL) was added and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated and then diluted with EtOAc (80 mL) and washed with saturated aqueous NaHCO₃ solution (2×20 mL). The organic layer was dried over MgSO₄, filtered and concentrated. The residue was chromatographed two times on

silica gel (230–400 mesh) using 50% EtOAc/DCM to give a glass. The glass was taken up in ethyl ether (5 mL) and upon standing at room temperature a solid formed and was collected by filtration, washed with ethyl ether (1 mL) and dried in a stream of air, to afford **TX63690** (69 mg) as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.46 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 2.65 (m, 1H), 2.48-2.58 (m, 2H), 1.99-2.12 (m, 2H), 1.72 (m, 1H), 1.43 (s, 3H), 1.28 (d, 3H, *J* = 6.8 Hz); *m/z*: [M+H]⁺ 336.0.

Compound 320b : Compound **130** (0.455 g, 1.28 mmol), K₃PO₄ (0.877 g, 4.14 mmol), 2-fluorophenylboronic acid (0.343 g, 2.48 mmol), dimethoxyethane (12 mL) and DMF (6 mL) were mixed and the mixture was sparged with N₂ for 3–5 min. Pd(PPh₃)₄ (0.126 g, 0.11 mmol) was added and the reaction was sparged again for 3–5 minutes. The vial was tightly sealed and heated at 95 °C for 2 days with stirring. The reaction was allowed to cool and was concentrated to dryness. The residue was partitioned between EtOAc (100 mL) and water (20 mL) and washed with saturated aqueous NaCl (20 mL), the layers were separated, the combined aqueous layers were washed with EtOAc (50 mL) and the combined organic layers dried over MgSO₄, filtered, concentrated and the residue was chromatographed on silica gel (230–400 mesh, 19.7 g) using 40% EtOAc/Hexanes as eluant to give **320b** (134.6 mg) as a clear glass, *m/z*: [M+H]⁺ 371.1.

Compound 321b: Compound **320b** (0.1346 g, 0.36 mmol) was taken up in MeOH (20 mL) and 1N HCl (3 mL) and the mixture was stirred 3 days at room temperature. The reaction mixture was concentrated to remove MeOH and then partitioned between EtOAc (50 mL) and saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated to afford **321b** (108 mg) as a foam/glass. *m/z*: [M+H]⁺ 327.1.

Compound 322b: Compound **321b** (0.108 g, 0.33 mmol) was taken up in ethyl formate (10 mL) and 30% NaOMe in MeOH (0.4 mL, 2.1 mmol) was added. The mixture was stirred overnight at room temperature, then partitioned between saturated aqueous KH₂PO₄ (10 mL) and EtOAc (80 mL). The organic layer was extracted with brine (10 mL) and dried over MgSO₄, filtered and concentrated to a glass (**322b**, 111 mg). *m/z*: [M+H]⁺ 355.1.

Compound 323b: A solution of 0.1 M hydroxylamine hydrochloride in 9:1 EtOH/H₂O (6 mL) was added to **322b** (0.111 g, 0.31 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to

remove ethanol, partitioned between EtOAc (100 mL) and saturated aqueous NaCl solution (10 mL) and the organic solution was dried over MgSO₄, filtered and concentrated to a glass (**323b**, 113 mg). *m/z*: [M+H]⁺ 352.1

Compound 324b: Compound **323b** (0.113 g, 0.32 mmol) was taken up in 1:1 MeOH/THF (6 mL) and 30% NaOMe in MeOH (0.3 mL, 1.6 mmol) was added. The mixture was stirred 3 days at room temperature, then partitioned between saturated KH₂PO₄ (15 mL) and EtOAc (100 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give **324b** (110.5 mg) as a foam. *m/z*: [M+H]⁺ 352.1.

Compound TX63721: Compound **324b** (0.1105 g, 0.31 mmol) was taken up in DMF (2 mL) and the mixture was cooled to 0 °C. *N,N'*-Dibromodimethylhydantoin (0.051 g, 0.18 mmol) was added and stirred until the starting material was consumed by thin layer chromatography. Pyridine (0.2 mL, 2.4 mmol) was added and the reaction mixture was warmed to room temperature, and was then heated at 60 °C for 2.5 hours. The reaction mixture was cooled and concentrated to dryness. The residue was chromatographed on silica gel (230–400 mesh, 16.6 g) using 3:1 Hexanes/EtOAc to give **TX63721** (45.7 mg) as an off-white foam. ¹H NMR (400 MHz, CDCl₃) δ 8.48 (s, 1H), 7.26–7.43 (m, 4H), 3.72 (s, 3H), 2.47–2.57 (m, 3H), 2.14 (m, 1H), 1.95 (m, 1H), 1.70 (m, 1H), 1.45 (s, 3H), 1.22 (d, 3H, *J* = 6.7 Hz); *m/z*: [M+H]⁺ 350.1.

Compound 320c: Compound **130** (0.450 g, 1.27 mmol), K₃PO₄ (0.866 g, 4.08 mmol), 4-pyridineboronic acid (0.310 g, 2.58 mmol), dimethoxyethane (12 mL) and DMF (6 mL) were mixed and the mixture was sparged with N₂ for 3–5 min. Pd(PPh₃)₄ (0.120 g, 0.10 mmol) was added and the reaction was sparged again for 3–5 minutes. Then the vial was tightly sealed and heated at 95 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was partitioned between EtOAc (100 mL) and water (20 mL) and washed with saturated aqueous NaCl (20 mL), the layers were separated, and the combined aqueous layers were washed with EtOAc (50 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated and the residue was chromatographed on silica gel (230–400 mesh, 20 g) using 3% MeOH/EtOAc as eluant to give **320c** (404.4 mg) as a white foam/solid, *m/z*: [M+H]⁺ 354.1.

Compound 321c: Compound **320c** (0.402 g, 1.14 mmol) was taken up in MeOH (25 mL) and 1N HCl (6 mL) and the mixture was stirred 3 days at room temperature. The reaction mixture was concentrated to remove MeOH and was then partitioned between EtOAc (80 mL) and saturated aqueous NaHCO₃ (15 mL). The

organic layer was dried over MgSO_4 , filtered and concentrated to a foam/glass (**321c**, 342 mg). m/z : $[\text{M}+\text{H}]^+$ 310.0.

Compound 322c: Compound **321c** (0.310 g, 1.0 mmol) was taken up in ethyl formate (30 mL), and 30% NaOMe in MeOH (1.2 mL, 6.5 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was partitioned between saturated aqueous KH_2PO_4 (40 mL) and EtOAc (100 mL). The aqueous layer was back-extracted with EtOAc (50 mL) and the combined organic layers were dried over MgSO_4 , filtered and concentrated to a glass (**322c**, 330 mg). m/z : $[\text{M}+\text{H}]^+$ 338.0.

Compound 323c: A solution of 0.1 M hydroxylamine hydrochloride in 9:1 EtOH/ H_2O (17.6 mL) was added to **322c** (0.330 g, 0.98 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to remove ethanol, partitioned between EtOAc (100 mL) and saturated aqueous NaHCO_3 solution (20 mL) and the organic solution was dried over MgSO_4 , filtered and concentrated to a foam (**323c**, 321 mg). m/z : $[\text{M}+\text{H}]^+$ 335.1.

Compound 324c: Compound **323c** (0.321 g, 0.96 mmol) was taken up in 1:1 MeOH/THF (20 mL) and 30% NaOMe in MeOH (1.0 mL, 5.4 mmol) was added. The mixture was stirred overnight at room temperature, and then partitioned between saturated KH_2PO_4 (20 mL) and EtOAc (150 mL). The organic layer was dried over MgSO_4 , filtered and concentrated to give **324c** (312 mg) as a foam. m/z : $[\text{M}+\text{H}]^+$ 335.1.

Compound TX63720: Compound **324c** (0.312 g, 0.93 mmol) was taken up in DCM (40 mL). DDQ (0.252 g, 1.11 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated to dryness, partitioned between EtOAc (150 mL), and the organic layer washed with saturated aqueous NaHCO_3 solution (50 mL). The aqueous layer was back-extracted with EtOAc (100 mL), and the combined organic layers were dried over MgSO_4 , filtered and concentrated. The residue was chromatographed on silica gel (230–400 mesh, 20 g) using 2% MeOH/DCM as eluant to give a greenish oil. The oil was triturated with Hexanes/ Et_2O to give **TX63720** (38.5 mg) as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.73 (bs, 2H), 8.45 (s, 1H), 7.29 (m, 2H), 3.85 (s, 3H), 2.50–2.70 (m, 3H), 1.98–2.14 (m, 2H), 1.72 (m, 1H), 1.44 ppm (s, 3H), 1.29 (d, 3H, $J = 6.7$ Hz); m/z : $[\text{M}+\text{H}]^+$ 333.1.

Compound 320d: Compound **130** (0.450 g, 1.27 mmol), K_3PO_4 (0.873 g, 4.12 mmol), 3-pyridineboronic acid (0.313 g, 2.61 mmol), dimethoxyethane (12 mL) and DMF (6 mL) were mixed and the mixture was sparged with N_2 for 3–5 min. Pd(PPh_3)₄ (0.124 g, 0.11 mmol) was added and the reaction was sparged again for 3–5 minutes. The vial was tightly sealed and heated at 95 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was partitioned between EtOAc (100 mL) and water (20 mL) and washed with saturated aqueous NaCl (20 mL). The combined aqueous layers were washed with EtOAc (50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (230–400 mesh, 20 g) using 3% MeOH/EtOAc as eluant to give **320d** (416 mg) as a white foam/glass, m/z : $[M+H]^+$ 354.1.

Compound 321d: Compound **320d** (0.413 g, 1.17 mmol) was taken up in MeOH (25 mL) and 1N HCl (6 mL) and the mixture was stirred 3 days at room temperature. The reaction mixture was concentrated to remove MeOH and was then partitioned between EtOAc (80 mL) and saturated aqueous $NaHCO_3$ (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to a foam/glass (**321d**, 338 mg). m/z : $[M+H]^+$ 310.0.

Compound 322d: Compound **321d** (0.303 g, 0.98 mmol) was taken up in ethyl formate (30 mL) and 30% NaOMe in MeOH (1.2 mL, 6.5 mmol) was added. The mixture was stirred overnight at room temperature, then partitioned between saturated aqueous KH_2PO_4 (40 mL) and EtOAc (100 mL). The aqueous layer was back-extracted with EtOAc (50 mL) and the combined organic layers were dried over KH_2PO_4 , filtered and concentrated to a glass (**322d**, 346 mg). m/z : $[M+H]^+$ 338.0.

Compound 323d: A solution of 0.1 M hydroxylamine hydrochloride in 9:1 EtOH/ H_2O (16 mL, 1.6 mmol) was added to **322d** (0.346 g, 1.03 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to remove ethanol, partitioned between EtOAc (100 mL) and saturated aqueous $NaHCO_3$ solution (20 mL) and the organic solution was dried over $MgSO_4$, filtered and concentrated to a foam/solid (**323d**, 299 mg). m/z : $[M+H]^+$ 335.1.

Compound 324d: Compound **323d** (0.289 g, 0.86 mmol) was taken up in 1:1 MeOH/THF (20 mL) and 30% NaOMe in MeOH (1.0 mL, 5.4 mmol) was added. The mixture was stirred overnight at room temperature, and was then partitioned between saturated KH_2PO_4 (20 mL) and EtOAc (150 mL). The organic layer was

dried over MgSO₄, filtered and concentrated to give **324d** (307 mg) as a foam. *m/z*: [M+H]⁺ 335.1.

Compound TX63722: Compound **324d** (0.307 g, 0.92 mmol) was taken up in DCM (40 mL) and DDQ (0.228 g, 1.004 mmol) was added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was filtered and the organic layer washed with saturated aqueous NaHCO₃ solution (50 mL), dried over MgSO₄, filtered and concentrated. The residue was chromatographed on silica gel (230–400 mesh, 18 g) using 1.5% MeOH/DCM as eluant to give a greenish oil. The oil was triturated with Hexanes/ Et₂O to give **TX63722** (40.3 mg) as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.67 (m, 1H), 8.61 (bs, 1H), 8.46 (s, 1H), 7.71 (m, 1H), 7.49 (m, 1H), 3.80 (s, 3H), 2.50–2.66 (m, 3H), 1.97–2.14 (m, 2H), 1.73 (m, 1H), 1.45 (s, 3H), 1.28 (d, 3H, *J* = 6.8 Hz); *m/z*: [M+H]⁺ 333.1.

Compound 320e: Compound **130** (0.453 g, 1.28 mmol), K₃PO₄ (0.882 g, 4.16 mmol), pyrimidine-5-boronic acid (0.315 g, 2.6 mmol), dimethoxyethane (12 mL) and DMF (6 mL) were mixed and the mixture was sparged with N₂ for 3–5 min. Pd(PPh₃)₄ (0.118 g, 0.10 mmol) was added and the reaction was sparged again for 3–5 minutes. The vial was tightly sealed and heated at 95 °C overnight with stirring. The reaction was cooled and concentrated to dryness. The residue was partitioned between EtOAc (100 mL) and brine (20 mL). The organic layer was dried over MgSO₄, filtered and concentrated and the residue was chromatographed on silica gel (230–400 mesh, 18 g) using 3% MeOH/EtOAc as eluant to give **320e** (333 mg) as an off-white solid, *m/z*: [M+H]⁺ 355.2.

Compound 321e: Compound **320e** (0.333 g, 0.94 mmol) was taken up in MeOH (25 mL) and 1N HCl (6 mL) was added. The mixture was stirred overnight at room temperature, then concentrated to remove MeOH and partitioned between EtOAc (80 mL) and saturated aqueous NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated to a solid (**321e**, 280.9 mg). *m/z*: [M+H]⁺ 311.2.

Compound 322e: Compound **321e** (0.2809 g, 0.91 mmol) was taken up in ethyl formate (34 mL) and 30% NaOMe in MeOH (1.05 mL, 5.7 mmol) was added. The mixture was stirred 3 days at room temperature, then partitioned between saturated aqueous KH₂PO₄ (20 mL) and EtOAc (100 mL). The organic layer was extracted with brine (10 mL), then dried over MgSO₄, filtered and concentrated to a glass (**322e**, 280 mg). *m/z*: [M+H]⁺ 339.1.

Compound 323e: A solution of hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in 10:1 EtOH/H₂O (22 mL) was added to **322e** (0.280 g, 0.83 mmol) and the mixture was stirred 3 days at room temperature. The reaction mixture was concentrated to dryness, and partitioned between EtOAc (100 mL) and saturated aqueous NaHCO₃ solution (10 mL). The organic solution was dried over MgSO₄, filtered and concentrated to a glass that solidified on standing. The solid was chromatographed on silica gel (230–400 mesh, 11 g) using EtOAc as eluant to afford **323e** (180 mg). *m/z*: [M+H]⁺ 336.1.

Compound 324e: Compound **323e** (0.180 g, 0.54 mmol) was taken up in 1:1 MeOH/THF (10 mL) and 30% NaOMe in MeOH (0.6 mL, 3.2 mmol) was added. The mixture was stirred overnight at room temperature, then partitioned between saturated KH₂PO₄ (15 mL) and EtOAc (120 mL). The organic layer was washed with saturated aqueous NaCl solution, dried over MgSO₄, filtered and concentrated to give **324e** (189 mg) as a foam. *m/z*: [M+H]⁺ 336.1.

Compound TX63748: Compound **324e** (0.189 g, 0.56 mmol) was taken up in DMF (2 mL) and the mixture was cooled to 0 °C. Bromine (0.092 g, 0.58 mmol) in DMF (0.5 mL) was added and stirred until the starting material was consumed by thin layer chromatography. Pyridine (0.45 mL, 5.6 mmol) was added and the reaction was warmed to room temperature, and then heated at 60 °C for 2 hours. The reaction mixture was cooled and concentrated to dryness. The residue was partitioned between EtOAc (100 mL) and saturated aqueous NaHCO₃ solution (50 mL), the layers separated, the organic layer dried over MgSO₄, filtered and concentrated to a yellow solid. The solid was triturated with ethyl ether and **TX63748** (108 mg) was collected by filtration as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H), 8.74 (s, 2H), 8.44 (s, 1H), 3.83 (s, 3H), 2.59 (m, 3H), 2.08 (m, 2H), 1.75 (m, 1H), 1.45 (s, 3H), 1.29 (d, 3H, *J* = 6.7 Hz); *m/z*: [M+H]⁺ 334.1.

Compound 325: A solution of **132** (431 mg, 1.4 mmol) and IBX (1.6 g, 5.6 mmol) in DMSO (7 mL) was heated at 65 °C for 7 h. The mixture was quenched with 50 mL of water and extracted with EtOAc (2×25 mL). The EtOAc extracts were concentrated, and purified by column chromatography (silica gel, 5–25% EtOAc/Hexanes) to give **325** as a white solid (189 mg, 43%). MS: *m/z* [M+H]⁺ 307.

Compound 326: A mixture of **325** (182 mg, 0.59 mmol), iodine (302 mg, 1.2 mmol) and pyridine (145 mg, 1.8 mmol) in THF (3 mL) was heated at 60 °C for 30 h. The reaction mixture was quenched with sodium thiosulfate (25 mL), extracted with

EtOAc (2×25 mL), washed with water, dried with MgSO₄ and concentrated to give **326** as a light colored solid (258 mg, 100%). MS: m/z [M+H]⁺ 433.

Compound TX63829: A mixture of **326** (254 mg, 0.58 mmol) and CuI (0.28 g, 1.4 mmol) in 5 mL of DMF was heated to 70 °C. FSO₂CF₂CO₂Me (1.7 g, 8.8 mmol) and HMPA (1.8 g, 10 mmol) were added sequentially, then kept at 70 °C for 6 h. The solvent was removed under vacuum and the crude product was purified by column chromatography (silica gel, 5–25% EtOAc/Hexanes) to give **TX63829** as a light yellow solid (95 mg, 42%). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.35–7.48 (m, 3H), 7.28–7.32 (m, 2H), 3.79 (s, 3H), 2.49–2.65 (m, 3H), 2.10 (dt, 1H, J = 2.0, 12.8 Hz), 1.95–2.02 (m, 1H), 1.64–1.77 (m, 1H), 1.44 (s, 3H), 1.26 (d, 3H, J = 6.8 Hz); MS: m/z [M+H]⁺ 375.

Compound 327: Compound **130** (0.54 g, 1.52 mmol) was taken up in DMA (6 mL) and zinc cyanide (120 mg, 1.02 mmol), dppf (169 mg, 0.30 mmol), and sodium carbonate (161 mg, 1.52 mmol) were added. Nitrogen was bubbled through the mixture for 10 min, then Pd(OAc)₂ (34 mg, 0.15 mmol) was added and nitrogen bubbling was continued for another 10 min. The mixture was then heated at 120 °C in a sealed vessel overnight. After cooling, water (25 mL) was added, and the mixture was extracted with ether (3×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give a brown semisolid. Flash chromatography (10% EtOAc/DCM) gave 0.41 g (90%) of **327** as a white solid. MS (APCI): m/z 302 [M+H]⁺.

Compound 328: Compound **327** (108 mg, 0.36 mmol) was taken up in THF (4 mL) and 1M HCl (1 mL) was added. The solution was stirred for 3 d, then diluted with sat. NaHCO₃ solution (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 91 mg (99%) of **328** as a white solid. MS (APCI): m/z 257.9 [M+H]⁺.

Compound 329: A solution of **328** (90 mg, 0.35 mmol) in THF (2 mL) and ethyl formate (2 mL) was cooled in an ice bath. NaOMe (0.6 g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath and quenched by the addition of sat. aq. KH₂PO₄ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated to give 105 mg (>100%) of **329** as a light yellow solid. MS (APCI): m/z 286 [M+H]⁺.

Compound 330: Compound **329** (0.35 mmol) was taken up in EtOH (2 mL), THF (2 mL), and water (0.5 mL). Hydroxylamine hydrochloride (27 mg, 0.38 mmol) was added and the reaction was stirred at room temperature for 30 min, and then heated at 50 °C overnight. An additional portion of hydroxylamine hydrochloride (5 mg) and heating was continued for an additional 4 h at 50 °C. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (20 mL) and 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 100 mg (100%) of **330** as a light yellow solid. MS (APCI): *m/z* 283 [M+H]⁺.

Compound 331: Compound **330** (100 mg, 0.35 mmol) was suspended in 3:1 THF/MeOH (4 mL) and NaOMe (0.6 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 4 h, then allowed to cool to room temperature and stirred overnight. The solution was concentrated and sat. aq. KH₂PO₄ (20 mL) was added. The mixture was extracted with EtOAc (2×50 mL) and the combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography (10% EtOAc/DCM) gave 71 mg (72%) of **331** as white solid. MS (APCI): *m/z* 283.1 [M+H]⁺.

Compound TX63725: Compound **331** (71 mg, 0.25 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (43 mg, 0.15 mmol) was added and the solution was stirred 90 min at 0 °C. Pyridine (0.4 mL) was added and the solution was heated at 60 °C for 5 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (5–10% EtOAc/DCM) gave 52 mg (74%) of **TX63725** as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 3.93 (s, 3H), 2.81 (ddd, 1H, *J* = 1.2, 6.4, 17.2 Hz), 2.60 (m, 1H), 2.48 (m, 1H), 1.92–2.06 (m, 2H), 1.67 (m, 1H), 1.34 (s, 3H), 1.24 (d, 3H, *J* = 6.7 Hz); MS (APCI): *m/z* 281.1 [M+H]⁺.

Compound 332: Compound **327** (0.29 g, 0.96 mmol) was taken up in toluene (5 mL) in a heavy-walled vessel. Trimethylsilylazide (0.25 mL, 1.92 mmol) was added followed by dibutyltin oxide (24 mg, 0.096 mmol). The vessel was sealed and heated overnight in a 130 °C oil bath. After cooling, MeOH (5 mL) was added and the solution was concentrated and dried under vacuum to give 0.45 g of a yellow glass. MS (APCI): *m/z* 345 [M+H]⁺. This material was taken up in DMF (5 mL), and K₂CO₃ (0.66 g, 4.81 mmol) was added followed by methyl iodide (0.30 mL, 4.81 mmol). The mixture was stirred overnight, water (25 mL) was added and the mixture

was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 0.40 g of a brown oil. Flash chromatography (50% EtOAc/Hexane) gave 147 mg (43%) of **332** as a white solid. MS (APCI): *m/z* 373.1 [M+H]⁺.

5 **Compound 333:** Compound **332** (177 mg, 0.49 mmol) was taken up in THF (4 mL) and 1M HCl (1 mL) was added. The solution was stirred for 3 d, diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 150 mg (97%) of **333** as a white solid. MS (APCI): *m/z* 315 [M+H]⁺.

10 **Compound 334:** A solution of **333** (95 mg, 0.29 mmol) in THF (2 mL) and ethyl formate (2 mL) was cooled in an ice bath. NaOMe (0.85 g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath and quenched by the addition of sat. aq. KH₂PO₄ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic
15 extracts were washed with brine, dried over MgSO₄, and concentrated to give 165 mg (100%) of **334** as a white solid. MS (APCI): *m/z* 343.1 [M+H]⁺.

Compound 335: Compound **334** (163 mg, 0.48 mmol) was suspended in EtOH (3 mL), THF (3 mL), and water (0.5 mL). Hydroxylamine hydrochloride (37 mg, 0.53 mmol) was added and the reaction was stirred at room temperature for 30
20 min, and then heated at 50 °C overnight. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (20 mL) and 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 145 mg (90%) of **335** as a white solid. MS (APCI): *m/z* 340.1 [M+H]⁺.

25 **Compound 336:** Compound **335** (145 mg, 0.43 mmol) was suspended in THF (4 mL) and MeOH (1 mL) and NaOMe (0.8 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 4 h, then allowed to cool to room temperature and concentrated. Sat. aq. KH₂PO₄ (20 mL) was added, and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine,
30 dried over MgSO₄, concentrated, and dried under vacuum to give 148 mg of a tan foam. Flash chromatography (1:3 EtOAc/DCM) gave 125 mg (86%) of **336** as an off-white solid. MS (APCI): 340.1 [M+H]⁺.

Compound TX63719: Compound **336** (125 mg, 0.37 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (63 mg,

0.22 mmol) was added and the solution was stirred 2 h at 0 °C. Pyridine (0.5 mL) was added and the solution was heated at 60 °C for 3 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography (10% EtOAc/DCM) gave 87 mg (70%) of **TX63719** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 4.41 (s, 3H), 4.20 (s, 3H), 3.06 (dd, 1H, *J* = 6.3, 17.3 Hz), 2.75 (ddd, 1H, *J* = 7.2, 11.6, 17.6 Hz), 2.55 (m, 1H), 2.01-2.13 (m, 2H), 1.76 (m, 1H), 1.44 (s, 3H), 1.30 (d, 3H, *J* = 6.7 Hz); MS (APCI): 338.1 [M+H]⁺.

Compound 337: Crude **332** (1.29 mmol) was taken up in pyridine (5 mL), and acetic anhydride (0.25 mL, 2.64 mmol) was added. The solution was heated at 110 °C for 3 h, then cooled and concentrated. The residue was diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 0.40 g of **337** as a dark brown oil. MS (APCI): *m/z* 359.2 [M+H]⁺.

Compound 338: Crude **337** (0.40 g, 1.12 mmol) was taken up in THF (5 mL) and 1M HCl (1 mL) was added. The solution was stirred for 3 d, diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated. Flash chromatography (75% EtOAc/Hexane) gave 70 mg (20%) of **338** as a white solid. MS (APCI): *m/z* 315.1 [M+H]⁺.

Compound 339: A solution of **338** (69 mg, 0.22 mmol) in THF (2 mL) and ethyl formate (1 mL) was cooled in an ice bath. NaOMe (0.4 g, 30 wt% in MeOH) was added dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was cooled in an ice bath, quenched by the addition of sat. aq. KH₂PO₄ (20 mL), and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 75 mg (100%) of **339** as a white solid. MS (APCI): *m/z* 343.1 [M+H]⁺.

Compound 340: Compound **339** (75 mg, 0.22 mmol) was taken up in 3:1 THF/EtOH (4 mL). Hydroxylamine (34 mg, 50 wt% solution in water) was added and the reaction was stirred for 1 h. Another portion of hydroxylamine (34 mg) was added and the solution was stirred overnight at room temperature. The solution was heated at 50 °C for 4 h, then cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (2×25 mL). The combined

organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give 70 mg of a tan foam. This material was suspended in benzene (3 mL) and *p*-TsOH (1 mg) was added. The mixture was heated at 70 °C for 8 h. After cooling, the solution was diluted with sat. aq. NaHCO₃ (20 mL) and
5 extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give 70 mg of a tan foam. Flash chromatography (1:2 EtOAc/DCM to 2:1 EtOAc/DCM) gave 35 mg (47%) of **340** as a white solid. MS (APCI): *m/z* 340.1 [M+H]⁺.

Compound 341: Compound **340** (35 mg, 0.10 mmol) was taken up in THF (2
10 mL) and MeOH (1 mL) and NaOMe (0.2 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 5 h, then cooled and concentrated. Sat. aq. KH₂PO₄ (10 mL) was added, and the mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, concentrated, and dried under vacuum to give 35 mg (100%) of **341** as a tan foam. MS (APCI): *m/z*
15 340.1 [M+H]⁺.

Compound TX63857: Compound **341** (35 mg, 0.10 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (17.7 mg, 0.062 mmol) was added and the solution was stirred 1 h at 0 °C. Pyridine (0.2 mL) was added and the solution was heated at 60 °C for 5 h. After cooling, the solution
20 was concentrated and dried under vacuum. Flash chromatography (20% EtOAc/DCM) gave 16 mg (46%) of **TX63857** as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 4.22 (s, 3H), 3.01 (dd, 1H, *J* = 6.4, 17.2 Hz), 2.68-2.82 (m, 1H), 2.61 (s, 3H), 2.49-2.59 (m, 1H), 2.00-2.13 (m, 2H), 1.69-1.84 (m, 1H), 1.43 (s, 3H), 1.30 (d, 3H, *J* = 6.8 Hz); MS (APCI): *m/z* 338.0 [M+H]⁺.

Compound 342: Compound **327** (0.71 g, 2.36 mmol) was suspended in EtOH (10 mL), and water (5 mL) was added followed by KOH (0.66 g, 11.8 mmol). The mixture was stirred for 4 d, and then poured into sat. KH₂PO₄ (50 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (25 mL), dried over MgSO₄, concentrated, and dried under vacuum to give 0.75 g (100%)
25 of **342** as a white solid. MS (APCI): *m/z* 320.1 [M+H]⁺.

Compound 343: Compound **342** (380 mg, 1.19 mmol) was added to DMAc-DMA (3 mL) and the mixture was heated at 80 °C for 3 h. The solution was cooled, concentrated, and dried under vacuum to give **343** as a white solid. MS (APCI): *m/z* 389.1 [M+H]⁺.

Compound 344: Hydroxylamine hydrochloride (124 mg, 1.78 mmol) was suspended in dioxane (4 mL) and Et₃N (0.25 mL, 1.78 mmol) was added. The mixture was sonicated for several minutes. A solution of **343** (1.19 mmol) in dioxane (4 mL) was added followed by acetic acid (0.36 g, 5.94 mmol). The mixture was heated at 80 °C for 2 h and allowed to cool to room temperature. The mixture was diluted with sat. NaHCO₃ (25 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (25 mL), dried over MgSO₄, concentrated, and dried under vacuum. Flash chromatography (5–20% EtOAc/DCM) gave 295 mg (69%) of **344** as a white solid. MS (APCI): *m/z* 359.1 [M+H]⁺.

Compound 345: Compound **344** (290 mg, 0.81 mmol) was taken up in THF (12 mL) and 1M HCl (3 mL) was added. The solution was stirred 4 d, then diluted with sat. NaHCO₃ (25 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (25 mL), dried over MgSO₄, concentrated, and dried under vacuum to give 246 mg (97%) of **345** as a white foam. MS (APCI): *m/z* 315.0 [M+H]⁺.

Compound 346: Compound **345** (230 mg, 0.73 mmol) was taken up in THF (6 mL) and ethyl formate (2 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 RT and stirred overnight. The mixture cooled in an ice bath, quenched by the addition of sat. aq. KH₂PO₄ (30 mL), and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (25 mL), dried over MgSO₄, concentrated, and dried under vacuum to give 250 mg (100%) of **346** as a light yellow solid. MS (APCI): *m/z* 343.0 [M+H]⁺.

Compound 347: Compound **346** (250 mg, 0.73 mmol) was suspended in THF (6 mL), EtOH (3 mL) and water (0.5 mL). Hydroxylamine hydrochloride (76 mg, 1.10 mmol) was added and the mixture was heated at 50 °C for 3 h. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (25 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (25 mL), dried over MgSO₄, concentrated, and dried under vacuum to give 250 mg (100%) of **347** as a light yellow foam. MS (APCI): *m/z* 340.1 [M+H]⁺.

Compound 348: Compound **347** (0.73 mmol) was taken up in 3:1 THF/MeOH (8 mL) and NaOMe (1.3 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 2 h, then allowed to cool to room temperature and concentrated. Sat. aq. KH₂PO₄ (40 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 MgSO₄, and concentrated to give 250 mg of a light yellow foam. Flash chromatography (10–15% EtOAc/DCM) gave 190 mg (77%) of **348** as a white foam. MS (APCI): *m/z* 340.1 [M+H]⁺.

5 **Compound TX63872:** Compound **348** (190 mg, 0.56 mmol) was taken up in DMF (5 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (96 mg, 0.34 mmol) was added and the solution was stirred 2 h at 0 °C. Pyridine (1 mL) was added and the solution was heated at 60 °C for 3 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash chromatography
10 (5% EtOAc/DCM) gave 150 mg (79%) of **TX63872** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 4.23 (s, 3H), 3.10 (dd, 1H, *J* = 6.0, 17.2 Hz), 2.75–2.86 (m, 1H), 2.48–2.60 (m, 1H), 2.46 (s, 3H), 2.00–2.15 (m, 2H), 1.69–1.83 (m, 1H), 1.43 (s, 3H), 1.30 (d, 3H, *J* = 6.8 Hz); MS (APCI): *m/z* 338.0 [M+H]⁺.

15 **Compound 349:** Diethyl oxalate (5 g, 10eq) was added to a suspension of NaH (0.51 g, 60% in oil) in THF (10 mL). A solution of **127** (0.8 g, 3.35 mmol) in THF (10 mL) was added. After refluxing for 16 h, the mixture was cooled, neutralized with sat. KH₂PO₄, and extracted with EtOAc (2×25 mL). The EtOAc was washed with brine and dried with MgSO₄ to give **349** (1.1 g, 100%). MS: *m/z* [M+H]⁺ 311.

20 **Compound 350:** A mixture of **349** (1.1 g, 3.35 mmol), methyl hydrazine (310 mg, 6.7 mmol), and EtOH (15 mL) was heated at 60 °C for 16 h. EtOH was removed, and the crude product was passed through a short packed silica gel column, eluted with 50% EtOAc/Hexanes, to give **350** as a white solid (220 mg, 19% yield). MS: *m/z* [M+H]⁺ 349.

25 **Compound 351:** A solution of the **350** (0.22 g, 0.63 mmol) in MeOH (5 mL) was treated with 3N HCl_(aq) (2 mL), stirred at RT overnight. The reaction mixture was concentrated, extracted with EtOAc (2×25 mL) and washed with sat'd NaHCO_{3(aq)} (25 mL). The organic layer was dried with MgSO₄, and concentrated to give **351** as a solid. (0.14 g, 73% yield). MS: *m/z* [M+H]⁺ 305.

30 **Compound 352:** To a solution of **351** (0.14 g, 0.46 mmol) in 5 mL of HCOOEt at RT was added 30% NaOMe in MeOH (0.4 g, 5 eq) dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat. KH₂PO₄. The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, concentrated in vacuo to give **352** (155 mg, 100% yield). MS: *m/z* [M+H]⁺ 333.

Compound 353: To a solution of **352** (155 mg, 0.46 mmol) in 10 mL of EtOH was added NH₂OH-HCl (75 mg, 2eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with
5 MgSO₄, concentrated in vacuo to give **353** (155 mg, 100%). MS: m/z [M+H]⁺ 330.

Compound 354: To a solution of **353** (155 mg, 0.46 mmol) in 2:1 THF/MeOH (3 mL) of was added MeOH, 30% NaOMe (0.95 g, 10 eq), and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with sat. KH₂PO₄ (25 mL) and extracted with EtOAc (2×25 mL). The
10 combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **354** (140 mg, 100% yield). MS: m/z [M+H]⁺ 302.

Compound 355: To a solution of **354** (140 mg, 0.46 mmol) in 2 mL of DMF at 0 °C was added DBDMH (92 mg, 0.55 eq), and the solution was stirred for 2 hours. Pyridine (0.4 g, 10 eq) was added, and the solution was heated at 50 °C overnight.
15 After concentration in vacuo, the residue was purified on a silica gel column, eluted with 25–100% EtOAc/Hexanes to give **355** as an off-white solid (110 mg, 80% yield). MS: m/z [M+H]⁺ 300.

Compound TX63655: To a solution of **355** (110 mg, 0.36 mmol) in 5 mL of THF at 0 °C, was added (COCl)₂ (350 mg, 6 eq) and 1 drop of DMF, and the solution
20 was stirred for 3 hours at RT. After evaporation of the solvent, the residue was dissolved in pyridine (5 mL), dimethylamine hydrochloride (450 mg, 10 eq) was added, and mixture was stirred at RT for 16 h. After evaporation of the pyridine, the crude product was purified by silica column chromatography, eluted with 15–50% EtOAc/Hexanes to give **TX63655** as an off-white solid (40 mg, 35% yield). ¹H NMR
25 (500 MHz, DMSO) δ 8.39 (s, 1H), 3.74 (s, 3H), 2.98 (s, 3H), 2.93 (s, 3H), 2.76-2.67 (m, 1H), 2.46-2.40 (m, 2H), 2.20-2.05 (t, 1H, J = 2.37, 12.3, 12.5), 1.95-1.85 (m, 1H), 1.65-1.60 (m, 1H), 1.38 (s, 3H), 1.20-1.12 (d, 3H, J = 6.61); MS: m/z [M+H]⁺ 327.

Compound 356: *n*-BuLi (1.6 M in hexane, 0.6 mL, 0.96 mmol) was added to DIPA (110 mg, 1.1 mmol) in THF (2 mL) at 0 °C, stirred for 30 min, and then the
30 reaction was cooled to –78 °C. Compound **TX63570** (0.2g, 0.68 mmol) in 1 mL of THF was added dropwise to the LDA solution. The reaction was stirred at –78 °C for 2 h and benzyl bromide (65 mg, 1.1 eq) in 1 mL of THF was added. After stirring for 2 h at 0 °C, the mixture was stirred at RT overnight. 1N HCl (2 mL) was added, reaction mixture was extracted with EtOAc (2×25 mL). The combined organic layers

were washed with water and brine. The crude product was purified by flash chromatography (silica gel, 5–30% EtOAc/Hexanes) to afford **356** as an oil (115 mg, 45%). MS (APCI): m/z $[M+H]^+$ 383.

Compound 357: Compound **356** (115 mg, 0.3 mmol) was dissolved in THF (15 mL) with 10% Pd/C (65 mg) at RT. The reaction mixture was treated with a hydrogen balloon and stirred for two days, filtered, and concentrated to give **357**, 105 mg. MS (APCI): m/z $[M+H]^+$ 385.

Compound 358: To a solution of **357** (105 mg, 0.27 mmol) in 5 mL of HCOOEt at RT, 30% NaOMe in MeOH (0.5 g, 10 eq) was added dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat. aq. KH_2PO_4 . The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give **358** (110 g, 98% yield). MS (APCI): m/z $[M+H]^+$ 413.

Compound 359: To a solution of **358** (105 mg, 0.26 mmol) in 5 mL of EtOH, $NH_2OH \cdot HCl$ salt (85 mg, 2 eq) was added, and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give **359** (110 mg, 100%). MS (APCI): m/z $[M+H]^+$ 410.

Compound 360: To a solution **359** (110 mg, 0.26 mmol) in 2:1 THF/MeOH (3 mL), 30% NaOMe (0.5 g, 5 eq) was added, and the solution was heated at 50 °C for 9 hours. After concentration in vacuo, the residue was mixed with KH_2PO_4 (sat., 15 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give **360** (110 mg, 100% yield). MS (APCI): m/z $[M+H]^+$ 410.

Compound TX63607: To a solution of **360** (110 mg, 0.26 mmol) in 2 mL of DMF at 0 °C, DBDMH (42 mg, 0.55 eq) was added, and the solution was stirred for 2 hours. Pyridine (1 g, 50 eq) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–30% EtOAc/Hexanes to give **TX63607** as an off-white solid (41 mg, 39% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.45–7.48 (m, 2H), 7.37–7.42 (m, 1H), 7.23–7.30 (m, 4H), 7.11–7.19 (m, 3H), 3.76 (s, 3H), 3.58 (br d, 1H, $J=15$ Hz), 3.07 (dd, 1H, $J=15, 5$ Hz), 2.84 (br d, 1H, $J=10$ Hz), 2.58 (dd, 1H, $J=20, 5$

Hz), 2.37-2.44 (m, 1H), 2.16-2.20 (m, 2H), 1.70-1.79 (m, 1H), 1.46 (s, 3H); MS (APCI): m/z $[M+H]^+$ 408.

Compound 361: A solution of KHMDS (658 mg, 3.30 mmol) in THF (6 mL) was cooled to $-60\text{ }^{\circ}\text{C}$. A solution of **TX63570** (482 mg, 1.65 mmol) in THF (4 mL) was added dropwise. The solution was allowed to warm slowly to $0\text{ }^{\circ}\text{C}$ and stirred 30 min. The solution was re-cooled to $-60\text{ }^{\circ}\text{C}$, and benzyl bromide (0.30 mL, 2.47 mmol) was added. The solution was allowed to warm to room temperature over 2 h. Sat. aq. NH_4Cl (20 mL) was added, and the mixture was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , and concentrated to give 0.67 g of a crude foam. Flash chromatography (10% EtOAc/DCM) gave 120 mg (15%) of **361** as a light yellow foam. MS (APCI): m/z $[M+H]^+$ 473.1 $[M+H]^+$.

Compound 362: Compound **361** (120 mg, 0.25 mmol) was dissolved in THF (15 mL) with 10% Pd/C (65 mg) at RT. The reaction mixture was treated with a hydrogen balloon and stirred for two days, filtered, and concentrated to give **362**, 120 mg. MS (APCI): m/z $[M+H]^+$ 475.

Compound 363: To a solution of **362** (120 mg, 0.25 mmol) in 4 mL of HCOOEt at RT, 30% NaOMe in MeOH (0.3 g, 6 eq) was added dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat. aq. KH_2PO_4 . The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , concentrated in vacuo to give **363** (120 mg, 95% yield). MS (APCI): m/z $[M+H]^+$ 503.

Compound 364: To a solution of **363** (120 mg, 0.23 mmol) in 5 mL of EtOH, $\text{NH}_2\text{OH}\cdot\text{HCl}$ (85 mg, 2 eq) was added and heated at $50\text{ }^{\circ}\text{C}$ overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , concentrated in vacuo to give **364** (120 mg, 100%). MS (APCI): m/z $[M+H]^+$ 500.

Compound 365: To a solution of **364** (120 mg, 0.23 mmol) in 2:1 THF/MeOH (3 mL), 30% NaOMe (0.5 g, 5 eq) was added, and the mixture was heated at $50\text{ }^{\circ}\text{C}$ for 12 hours. After concentration in vacuo, the residue was mixed with KH_2PO_4 (sat., 15 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO_4 , concentrated in vacuo to give **365** (115 mg, 98% yield). MS (APCI): m/z $[M+H]^+$ 500.

Compound TX63601: To a solution of **365** (115 mg, 0.23 mmol) in 2 mL of DMF at 0 °C, DBDMH (38 mg, 0.55 eq) was added, and the solution was stirred for 2 hours. Pyridine (1 g, 55 eq) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel
5 column (5–30% EtOAc/Hexanes) to give **TX63601** as an off-white solid (31 mg, 28% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.35 (s, 1H), 7.40-7.48 (m, 3H), 7.25-7.31 (m, 5H), 7.09-7.18 (m, 5H), 6.91 (d, 2H, J=10 Hz), 3.74 (s, 3H), 3.28 (d, 1H, 15 Hz), 3.18 (d, 1H, J=15 Hz), 2.92 (d, 1H, J=15 Hz), 2.62-2.69 (m, 2H), 2.36-2.43 (m, 2H), 2.16 (dd, 1H, J=15, 5 Hz), 2.02-2.08 (m, 1H), 1.65 (s, 3H); MS (APCI): *m/z* [M+H]⁺ 498.

Compound 366: A solution of diisopropylamine (0.30 mL, 2.15 mmol) in THF (2 mL) was cooled to –78 °C, and BuLi (1.6 M in hexane, 1.35 mL, 2.15 mmol) was added dropwise. The solution was removed from the cooling bath and stirred 15 min. The solution was re-cooled to –78 °C and a solution of **TX63570** (0.21 g, 0.72 mmol) in THF (3 mL) was added dropwise. The solution was stirred 15 min, then
15 transferred to an ice bath and stirred 30 min. The solution was re-cooled to –78 °C, and a suspension of diphenyliodonium chloride (0.227 g, 0.72 mmol) in DMF (8 mL) was added. The solution was stirred 1 h at –78 °C, then allowed to warm to room temperature and stirred 3 h. The solution was quenched with sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed
20 with brine (20 mL), dried over MgSO₄, and concentrated to give 0.33 g of a brown oil. Flash chromatography (25% EtOAc/DCM) gave 80 mg (31%) of **366** as white foam. MS (APCI): *m/z* 369 [M+H]⁺.

Compound 367: Compound **366** (76 mg, 0.019 mmol) was taken up in THF (5 mL) and 10% Pd/C (20 mg) was added under nitrogen. The mixture was evacuated
25 and purged with H₂ (3×), and stirred under a H₂ balloon overnight. The mixture was filtered through a fine frit, and the filtrate was concentrated to give 80 mg (>100%) of **367** as a white foam. MS (APCI): *m/z* 371.1 [M+H]⁺.

Compound 368: A solution of **367** (75 mg, 0.20 mmol) in ethyl formate (5 mL) was cooled in an ice bath. NaOMe (0.55 g, 30 wt% in MeOH) was added
30 dropwise, and the solution was allowed to warm to RT and stirred overnight. The mixture was quenched by the addition of sat. aq. KH₂PO₄ (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated to give 90 mg (>100%) of **368** as a tan foam. MS (APCI): *m/z* 399 [M+H]⁺.

Compound 369: Compound **368** (0.20 mmol) was taken up in EtOH (3 mL) and water (0.5 mL). Hydroxylamine hydrochloride (15 mg, 0.22 mmol) was added and the reaction was heated at 60 °C for 3 h. The solution was cooled and concentrated. The residue was diluted with sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, and concentrated to give 90 mg (>100%) of **369** as a tan foam. MS (APCI): m/z 396 [M+H]⁺.

Compound 370: Compound **369** (0.20 mmol) was taken up in 2:1 THF:MeOH (3 mL) and NaOMe (0.3 g, 30 wt% in MeOH) was added. The solution was heated at 50 °C for 4 h, and then allowed to cool to room temperature. Sat. aq. KH₂PO₄ (10 mL) was added, and the mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography (1:2 EtOAc/DCM) gave 72 mg (91%) of **370** as an off-white solid. MS (APCI): m/z 396.1 [M+H]⁺.

Compound TX63629: Compound **370** (71 mg, 0.18 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (31 mg, 0.11 mmol) was added and the solution was stirred 2 h at 0 °C. Pyridine (0.2 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, the solution was concentrated under vacuum to a brown solid. Flash chromatography (20% EtOAc/DCM) gave 56 mg (79%) of **TX63629** as a pale yellow solid. MS (APCI): ¹H NMR (500 MHz, CDCl₃) δ 8.65 (s, 1H), 7.52-7.26 (m, 8H), 7.14 (m, 2H), 3.84 (s, 3H), 3.68 (d, 1H, J = 13.6), 2.72 (m, 1H), 2.54-2.39 (m, 2H), 2.67 (m, 1H), 1.63 (s, 3H), 1.46 (m, 1H); m/z 394.1 [M+H]⁺.

Compound 371: Dimethyl carbonate (3.1 g, 10 eq) was added to a suspension of NaH (0.51 g, 60% in oil) in THF (10 mL). A solution of **127** (0.8 g, 3.35 mmol) in THF (10 mL) was added. After refluxing for 16 h, the solution was cooled, neutralized with KH₂PO₄ (conc.), and extracted with EtOAc (2×25 mL). The EtOAc was washed with brine and dried with MgSO₄ to give crude compound **371** (1 g, 100%). MS: m/z [M+H]⁺ 297.

Compound 372: A solution of acetimidamide hydrochloride (3.2 g, 10 eq) and piperidine (1.45 g, 5 eq) in 10 mL of *i*-PrOH was stirred at RT for 15 min. Crude **371** (1 g, 3.35 mmol) in 5 mL of 2-propanol was added slowly, and stirred at RT for 30 min. The reaction mixture was heated at reflux for two days, then concentrated. The reaction mixture was mixed with ether (50 mL). The product was precipitated,

filtered and washed with water, to give **372** as an off-white solid (425 mg, 42% yield). MS: m/z $[M+H]^+$ 305.

Compound 373: To a suspension of **372** (0.4 g, 1.3 mmol) in phosphorus oxychloride (10 mL, 107 mmol) was added two drops of DMF at RT. The resulting mixture was stirred at 140 °C for 3 h. The mixture was then concentrated to dryness, diluted with EtOAc (50 mL) and washed with NaHCO₃ (50 mL) and water (50 mL). The organic layer was separated, dried (MgSO₄) and evaporated to dryness. Compound **373** was obtained as a crude yellow oil (385 mg, 100%) and was used without further purification.

Compound 374: 30% NaOMe (1.2 g, 5 eq) in MeOH was added dropwise to a stirred solution of **373** in dry MeOH (10 mL). The solution was heated at 50 °C for 3h. The mixture was then concentrated to dryness, diluted with EtOAc (35 mL) and washed with sat. KH₂PO₄ (25 mL), followed by brine, dried (MgSO₄) and solvents removed. Purification by silica gel column chromatography using (5–40% EtOAc/Hexanes gradient) gave **374** as an oil (155 mg, 44% yield). MS: m/z $[M+H]^+$ 275.

Compound 375: To a solution of **374** (155 mg, 0.56 mmol) in 5 mL of HCOOEt was added 30% NaOMe in MeOH (1 g, 10 eq) dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with sat. KH₂PO₄. The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **375**. (170 mg, 100% yield). MS: m/z $[M+H]^+$ 303.

Compound 376: To a solution of **375** (170 mg, 0.56 mmol) in 10 mL of EtOH was added NH₂OH·HCl salt (80 mg, 2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, concentrated in vacuo to give **376** (170 mg, 100% yield). MS: m/z $[M+H]^+$ 300.

Compound 377: To a solution of **376** (170 mg, 0.56 mmol) in 2 mL of THF and 1 mL of MeOH was added 30% NaOMe (1 g, 10eq), and the solution was heated at 50 °C for 9 hours. After concentration in vacuo, the residue was mixed with sat. KH₂PO₄ (15 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, concentrated in vacuo to give **377** (170 mg, 100% yield). MS: m/z $[M+H]^+$ 300.

Compound TX63646: To a solution of **377** (170 mg, 0.56 mmol) in 2 mL of DMF at 0 °C, was added DBDMH (90 mg, 0.55 eq), and the solution was stirred for 2 hours. Pyridine (1 g) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with
5 15–40% EtOAc/Hexanes to collect **TX63646** as an off-white solid (50 mg, 30% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.92 (s, 1H), 4.00 (s, 3H), 2.80 (dd, 1H, *J* = 6.7, 18.3 Hz), 2.61 (s, 3H), 2.52–2.60 (m, 2H), 2.04–2.16 (m, 2H), 1.73 (m, 1H), 1.41 (s, 3H), 1.32 (d, 3H, *J* = 6.7 Hz); MS: *m/z* [M+H]⁺ 398.

Compound 378: In a sealable vial, a solution of sl. impure **371** (crude from
10 previous step, assume 3.36 mmol) in 20 mL of *i*-PrOH was treated with solid cyclopropanecarboximidamide hydrochloride (4.05 g, 33.59 mmol) followed by piperidine (1.7 mL, 17.2 mmol). The sample was flushed with N₂, sealed and heated (via a block heater) at 90 °C for 72 h. The sample was cooled, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was
15 washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 50% EtOAc/Hexanes) to give 0.85 g (77%) of **378** as an off-white solid. MS (APCI) *m/z* 331 (100%) [M+H]⁺.

Compound 379: A solution of **378** (0.85 g, 2.58 mmol) in 10 mL of MeOH and 3N HCl (10 mL, 30 mmol) was stirred at room temperature under N₂ for 16 h.
20 The sample was concentrated, cooled, basified with 10% aq. NH₄OH solution to a pH ~ 9–10 and extracted with CHCl₃. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.70 g (94%) of **379** as an off-white solid. MS (APCI) *m/z* 287 (100%) [M+H]⁺.

Compound 380: To a stirring solution of **379** (0.70 g, 2.43 mmol) and *N,N*-diisopropylethylamine (0.47 mL, 2.70 mmol) in 24 mL of benzene was added
25 dropwise (via syringe) phosphorus oxychloride (2.3 mL, 24.6 mmol). After addition, the sample was heated at 80 °C under N₂ for 16 h, cooled, concentrated then carefully partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.69
30 g (94%) of **380** as an off-white solid. MS (APCI) *m/z* 305/307 (100/47%) [M+H]⁺.

Compound 381: A solution at room temperature under N₂ of **380** (0.32 g, 1.07 mmol) in 10 mL of THF:MeOH (1:1) was treated with NaOMe, 30 wt% solution in MeOH (2.0 mL, 10.7 mmol). The sample was heated at 50 °C for 2 h, cooled, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic

extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.34 g (>100%) of sl. impure **381** as a yellow oil, which was used without purification.

Compound 382: To a stirring solution of sl. impure **381** (0.34 g, assume 1.07 mmol) and ethyl formate (9.0 mL, 111.0 mmol) in 10 mL of benzene was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (2.0 mL, 10.7 mmol). The sample was stirred at room temperature under N₂ for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.35 g (>100%) of sl. impure **382** as a dark yellow oil, which was used without purification.

Compound 383: A solution of sl. impure **382** (0.35 g, assume 1.07 mmol) and hydroxylamine hydrochloride (0.11 g, 1.58 mmol) in 25 mL of EtOH was heated at 50 °C under N₂ for 2 h then room temperature overnight. The sample was concentrated and partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.31 g (90%) of sl. impure **383** as a tan foamy solid, which was used without purification. MS (ES) *m/z* 326 (100%) [M+H]⁺.

Compound 384: To a stirring solution of sl. impure **383** (0.31 g, 0.96 mmol) at room temperature under N₂ in 20 mL of MeOH was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (0.90 mL, 4.80 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give 0.13 g (41%) **384** as an off-white foamy solid.

Compound TX63761: To a stirring solution at 0 °C under N₂ of **384** (0.13 g, 0.40 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.057 g, 0.20 mmol). After stirring at 0 °C for 1 h, pyridine (0.33 mL, 4.08 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 3 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. KH₂PO₄ and sat. NaCl solutions, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give 0.030 g (23%) of **TX63761** as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.88

(s, 1H), 3.94 (s, 3H), 2.75 (dd, 1H, $J = 7.0, 18.2$ Hz), 2.52 (m, 2H), 2.16 (m, 1H), 2.06 (m, 2H), 1.68 (dq, 1H, $J = 6.5, 12.8$ Hz), 1.38 (s, 3H), 1.29 (d, 3H, $J = 6.8$ Hz), 1.10 (m, 2H), 1.02 (m, 2H); MS (APCI) m/z 324 (100%) $[M+H]^+$.

Compound 385: In a sealable vial, a solution of **371** (crude from previous
5 step, assume 4.20 mmol) in 15 mL of *n*-BuOH was treated with solid 2,2-
dimethylpropionamidinium hydrochloride (5.0 g, 36.6 mmol) followed by piperidine
(2.1 mL, 21.2 mmol). The sample was flushed with N₂, sealed and heated (via a
block heater) at 100 °C for 72 h. The sample was cooled, concentrated then
partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was
10 washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and
chromatographed (silica gel, 50% EtOAc/Hexanes) to give 0.87 g (60%) of **385** as a
tan gummy solid. MS (APCI) m/z 347 (100%) $[M+H]^+$.

Compound 386: A solution of **385** (0.87 g, 2.50 mmol) and *N,N*-
diisopropylethylamine (0.48 mL, 2.76 mmol) in 10 mL of benzene was added
15 dropwise (via syringe) phosphorus oxychloride (2.3 mL, 24.7 mmol). After addition,
the sample was heated at 90 °C under N₂ for 2 h then room temperature overnight.
The sample was concentrated then carefully partitioned between EtOAc and sat.
NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried
(MgSO₄), filtered and concentrated to give 0.85 g (93%) of **386** as a light yellow oil,
20 which was used without purification. MS (APCI) m/z 365/367 (100/38%) $[M+H]^+$.

Compound 387: A solution of **386** (0.42 g, 1.16 mmol) in 10 mL of MeOH
was treated with NaOMe, 30 wt% solution in MeOH (1.1 mL, 5.9 mmol). The
sample was flushed with N₂, sealed and heated at 80 °C for 48 h. The sample was
cooled, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The
25 organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and
concentrated to give 0.42 g (~100%) of **387** as a dark yellow oil, which was used
without purification.

Compound 388: A solution of **387** (0.42 g, 1.16 mmol) and 3N HCl (10 mL,
30 mmol) in 10 mL of MeOH was stirred at room temperature under N₂ for 16 h. The
30 sample was concentrated, cooled, basified with 10% aq. NH₄OH solution to a pH ~9–
10 and extracted with EtOAc. The organic extract was washed with sat. NaCl
solution, dried (MgSO₄), filtered and concentrated to give 0.34 g (92%) of **388** as a
yellow solid, which was used without purification. MS (APCI) m/z 317 (100%)
 $[M+H]^+$.

Compound 389: To a stirring solution of **388** (0.34 g, 1.07 mmol) and ethyl formate (10 mL, 124 mmol) in 10 mL of benzene was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (1.0 mL, 5.3 mmol). The sample was stirred at room temperature under N₂ for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.36 g (97%) of **389** as a dark yellow oil, which was used without purification. MS (APCI) *m/z* 345 (100%) [M+H]⁺.

Compound 390: A solution of **389** (0.36 g, 1.04 mmol) and hydroxylamine hydrochloride (0.11 g, 1.58 mmol) in 10 mL of EtOH was heated at 50 °C under N₂ for 2 h then room temperature overnight. The sample was concentrated and partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.59 g (>100%) of **390** as a dark yellow oil, which was used without purification.

Compound 391: To a stirring solution of sl. impure **390** (crude from previous step, assume 1.04 mmol) at room temperature under N₂ in 10 mL of MeOH:THF (1:1) was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (0.98 mL, 5.22 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 20% EtOAc/Hexanes) to give 0.18 g (50%) **391** as a light yellow oil. MS (APCI) *m/z* 342 (100%) [M+H]⁺.

Compound TX63853: To a stirring solution at 0 °C under N₂ of **391** (0.18 g, 0.52 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.075 g, 0.26 mmol). After stirring at 0 °C for 1 h, pyridine (0.42 mL, 5.20 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 20% EtOAc/Hexanes) to give 0.068 g (38%) of **TX63853** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.60 (s, 1H), 3.97 (s, 3H), 2.76 (dd, 1H, *J* = 6.4, 18.0 Hz), 2.51-2.60 (m, 2H), 2.00-2.15 (m, 2H), 1.60-1.75 (m, 1H), 1.36 (s, 12H), 1.28 (d, 3H, *J* = 6.8 Hz); MS (APCI) *m/z* 340 (100%) [M+H]⁺.

Compound 392: KOt-Bu (250 mg, 1eq) was dissolved in anhydrous EtOH (20 mL). Thiourea (1.7 g, 10 eq) and **371** (950 mg, 3.2 mmol) were added to the base solution. The reaction mixture was refluxed for 16 h. The solvent concentrated under vacuo to nearly dryness and the residue was redissolved in water (10 mL). The solution was neutralized with 3N HCl, the precipitate was collected, washed with water, and dried under vacuum to give **392** (900 mg, 87% yield). MS: m/z $[M+H]^+$ 323.

Compound 393: Compound **392** (900 mg, 2.79 mmol) was dissolved in DMF (10 mL), and K₂CO₃ (1.2 g, 3eq) was added, and the mixture was stirred for 30 min. MeI (0.8 g, 2 eq) was added dropwise, and the mixture was stirred at RT for 2 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (2×50 mL). The organic layer was washed with water and brine, and concentrated to give **393** (975 mg, 100% yield). MS: m/z $[M+H]^+$ 351.

Compound 394: To a stirred mixture of **393** (975 mg, 2.79 mmol) and Pd(PPh₃)₄ (200 mg, 5 mol%) in THF (20 mL) under nitrogen, phenylboronic acid (1 g, 3eq) and CuTC (1.8 g, 3.5 eq) were added. The reaction mixture was heated at reflux for 16 h. The solvent was removed in vacuo and the residue was purified by a silica gel column chromatography, eluted with 10–35% EtOAc/Hexanes to give **394** as a solid (415 mg, 40% yield). MS: m/z $[M+H]^+$ 381.

Compound 395: A solution of **394** (455 mg, 1.2 mmol) in MeOH (10 mL) was treated with 3N HCl_(aq) (3 mL), and stirred at RT overnight. The reaction mixture was concentrated, extracted by EtOAc (2×25 mL) and washed with sat'd NaHCO_{3(aq)} (25 mL). The organic layer was dried with MgSO₄, and concentrated to give **395** as an oil (405 mg, 100% yield). MS: m/z $[M+H]^+$ 337.

Compound 396: To a solution of **395** (405 mg, 1.2 mmol) in 5 mL of HCOOEt was added dropwise 30% NaOMe in MeOH (1.3 g, 6 eq). The reaction mixture was stirred at RT overnight, then poured into water and acidified with sat. KH₂PO₄. The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with MgSO₄, concentrated in vacuo to give **396** (435 mg, 100% yield). MS: m/z $[M+H]^+$ 365.

Compound 397: To a solution of **396** (435 mg, 1.18 mmol) in 20 mL of EtOH was added NH₂OH·HCl salt (170 mg, 2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with

brine, dried with MgSO_4 , and concentrated in vacuo to give **397** (430 mg, 98% yield). MS: m/z $[\text{M}+\text{H}]^+$ 362.

Compound 398: To a solution of **397** (430 mg, 1.18 mmol) in 2 mL of THF and 2 mL of MeOH was added 30% NaOMe (1.7 g, 8 eq), and the solution was heated
5 at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with sat. KH_2PO_4 (25 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with water and brine, dried with MgSO_4 , and purified on a silica gel column, eluted with 15–45% EtOAc/Hexanes to give **398** as an off-white solid (215 mg, 50% yield). MS: m/z $[\text{M}+\text{H}]^+$ 362.

Compound TX63666: To a solution of **398** (210 mg, 0.58 mmol) in 2 mL of DMF at 0 °C was added 1,3-dibromo-5,5-dimethylhydantoin (95 mg, 0.55 eq), and the solution was stirred for 2 hours. Pyridine (1 g) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 15–45% EtOAc/Hexanes to give **TX63666** as an off-
15 white solid (130 mg, 62% yield). ^1H NMR (500 MHz, CDCl_3) δ 8.76 (s, 1H), 7.58 (m, 5H), 3.50 (s, 3H), 2.90 (m, 1H), 2.52–2.61 (m, 2H), 2.05–2.20 (m, 2H), 1.72 (m, 1H), 1.45 (s, 3H), 1.34 (d, 3H, $J = 6.6$ Hz); MS: m/z $[\text{M}+\text{H}]^+$ 360.

Compound 399: A mixture of **392** (2.6g, 8.06 mmol) and 8.1 g of chloroacetic acid (10 eq) was heated at 100 °C for 1 h, then 10 mL of water was
20 added and heating continued for another 5 h. Concentrated HCl (0.5 mL) was added and the mixture was heated at 100 °C for 16 h. The reaction was cooled and 50 mL of ice water was added. The precipitate was collected by filtration, and dried under vacuum to give **399** as an off-white solid (2.1 g, 93% yield). MS: m/z $[\text{M}+\text{H}]^+$ 263.

Compound 400: A mixture of **399** (2.03 g, 7.73 mmol) and
25 diisopropylethylamine (1.01 g, 1 eq) in 10 mL of POCl_3 was heated at 90 °C for 16 h. The reaction was quenched with ice and the product was precipitated, filtered and dried under vacuum to give **400** as a brown solid (2.1 g, 90% yield). MS: m/z 299, 301 (3:2) $[\text{M}+\text{H}]^+$.

Compound 401a-b: A solution of **400** (2.05 g, 6.85 mmol), NaOMe (1.85 g, 1.5 eq, 30% in MeOH) and 25 mL of MeOH was heated at 50 °C for 1 h. The reaction
30 mixture was concentrated, extracted with EtOAc (2×20 mL), washed with water, and purified on a silica gel column, with 10–15% EtOAc/Hexanes elution. The first compound obtained was **401a** (1.3 g, 65% yield), MS: m/z 295, 297 (3:1) $[\text{M}+\text{H}]^+$.

The second compound obtained was **401b** (110 mg, 5.5% yield), MS: m/z 291 $[M+H]^+$.

Compound 402: To a solution of **401a** (130 mg, 0.44 mmol) in 5 mL of HCOOEt was added dropwise 30% NaOMe in MeOH (0.5 g, 6 eq). The reaction mixture was stirred at RT overnight, then poured into water and acidified with KH_2PO_4 . The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give **402** (140 mg, 100% yield). MS: m/z $[M+H]^+$ 319.

Compound 403: To a solution of **402** (140 mg, 0.44 mmol) in 10 mL of EtOH was added $NH_2OH \cdot HCl$ salt (65 mg, 2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **403** (138 mg, 100% yield). MS: m/z $[M+H]^+$ 316.

Compound 404: To a solution of **403** (138 mg, 0.44 mmol) in 2 mL of THF and 1 mL of MeOH was added dropwise 30% NaOMe (0.63 g, 8 eq), and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with sat. KH_2PO_4 (15 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **404** (136 mg, 100% yield). MS: m/z $[M+H]^+$ 316.

Compound TX63718: To a solution of **404** (136 mg, 0.44 mmol) in 2 mL of DMF at 0 °C was added 1,3-dibromo-5,5-dimethylhydantoin (70 mg, 0.55 eq), and the solution was stirred for 2 hours. Pyridine (1 g) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–30% EtOAc/Hexanes to give **TX63718** as an off-white solid (55 mg, 40% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 2.67 (dd, 1H, $J = 7.0, 17.5$ Hz), 2.37-2.51 (m, 2H), 1.95-2.06 (m, 2H), 1.62 (m, 1H), 1.33 (s, 3H), 1.22 (d, 3H, $J = 6.5$ Hz); MS: m/z $[M+H]^+$ 314.

Compounds TX63793 and TX63794: The enantiomers of compound **TX63718** (32.7 mg) were separated using chiral HPLC (CHIRALPAK IA, 5 μ , 30×250 mm, 2:50:50 EtOH/EtOAc/Hexane) to afford two well resolved two peaks. One is at 4.04 min, which gave **TX63793** (17.6 mg, >99.9% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 2.75 (dd, 1H, $J = 6.4, 18.0$ Hz), 2.52 (m, 2H), 2.09 (m, 2H), 1.70 (m, 1H), 1.41 (s, 3H), 1.30 (d, 3H, $J = 6.7$ Hz). And

another one is at 4.66 min, which gave **TX63794** (15.1 mg, 98.8% ee). ¹H NMR (400 MHz, CDCl₃) δ 8.79 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 2.75 (dd, 1H, *J* = 6.4, 18.0 Hz), 2.52 (m, 2H), 2.09 (m, 2H), 1.70 (m, 1H), 1.41 (s, 3H), 1.30 (d, 3H, *J* = 6.7 Hz).

Compound 405a: Compound **401b** (0.25 g, 0.84 mmol) was dissolved in
5 DME (6 mL) and DMF (3 mL). To this solution was added pyridin-3-ylboronic acid (125 mg, 1 mmol), Ph₃P (85 mg, 0.32 mmol) and K₃PO₄ (0.54 g, 2.54 mmol). Nitrogen was bubbled through the mixture for 10 min. Pd(OAc)₂ (35 mg, 0.16 mmol) was added and nitrogen bubbled for another 10 min. The suspension was heated to 90 °C for 16 hours. The reaction mixture was filtered, concentrated, and purified on a
10 silica gel column, eluted with 5–35% EtOAc/Hexanes to give **405a** as a solid (0.28 g, 98% yield). MS: *m/z* [M+H]⁺ 338.

Compound 405b: Pyridin-4-ylboronic acid (125 mg, 1 mmol) was treated according to the procedure for compound **401b** to give **405bb** (270 mg, 95% yield). MS: *m/z* [M+H]⁺ 338.

15 **Compound 405c:** 2-Methoxyphenylboronic acid (155 mg, 1 mmol) was treated according to the procedure for compound **401b** to give **405c** (150 mg, 49% yield). MS: *m/z* [M+H]⁺ 367.

Compound 405d: Phenylboronic acid (155 mg, 1 mmol) was treated according to the procedure for compound **401b** to give **405d** (185 mg, 65% yield).
20 MS: *m/z* [M+H]⁺ 337.

Compound 405e: Pyrimidin-5-ylboronic acid (140 mg, 1.13 mmol) was treated according to the procedure for compound **401b** to give **405e** (185 mg, 58% yield). MS: *m/z* [M+H]⁺ 339.

Compound 406a: To a solution of **405a** (280 mg, 0.82 mmol) in 10 mL of
25 HCOOEt was added dropwise 30% NaOMe in MeOH (6 eq). The reaction mixture was stirred at RT overnight, then poured into water and acidified with KH₂PO₄. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo to give **406a** (300 mg). MS: *m/z* [M+H]⁺ 366.

30 **Compound 406b:** Compound **405b** (270 mg, 0.82 mmol) was treated according to the procedure for compound **406a** to give the title compound **406b** (290 mg). MS: *m/z* [M+H]⁺ 366.

Compound 406c: Compound **405c** (150 mg, 0.4 mmol) was treated according to the procedure for compound **406a** to give the title compound **406c** (120 mg). MS: m/z $[M+H]^+$ 395.

5 **Compound 406d:** Compound **405d** (185 mg, 0.51 mmol) was treated according to the procedure for compound **406a** to give the title compound **406d** (185 mg). MS: m/z $[M+H]^+$ 365.

Compound 406e: Compound **405e** (175 mg, 0.51 mmol) was treated according to the procedure for compound **406a** to give the title compound **406e** (185 mg). MS: m/z $[M+H]^+$ 367.

10 **Compound 407a:** To a solution of **406a** (300 mg, 0.82 mmol) in 20 mL of EtOH was added $NH_2OH \cdot HCl$ salt (2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **407a** (280 mg). MS: m/z $[M+H]^+$ 363.

15 **Compound 407b:** Compound **406b** (290 mg, 0.79 mmol) was treated according to the procedure for compound **407a** to give the title compound **407b** (290 mg). MS: m/z $[M+H]^+$ 363.

Compound 407c: Compound **406c** (120 mg, 0.3 mmol) was treated according to the procedure for compound **407a** to give the title compound **407c** (117 mg). MS: m/z $[M+H]^+$ 392.

20 **Compound 407d:** Compound **406d** (130 mg, 0.34 mmol) was treated according to the procedure for compound **407a** to give the title compound **407d** (120 mg). MS: m/z $[M+H]^+$ 376.

Compound 407e: Compound **406e** (185 mg, 0.5 mmol) was treated according to the procedure for compound **407a** to give the title compound **407e** (180 mg). MS: m/z $[M+H]^+$ 364.

25 **Compound 408a:** To a solution of compound **407a** (280 mg, 0.78 mmol) in 4 mL of THF and 2 mL of MeOH was added dropwise 30% NaOMe (8 eq), and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with sat. KH_2PO_4 solution (30 mL) and extracted with EtOAc. The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **408a** (220 mg). MS: m/z $[M+H]^+$ 363.

Compound 408b: Compound **407b** (290 mg, 0.79 mmol) was treated according to the procedure for compound **408a** to give the title compound **408b** (280 mg). MS: m/z $[M+H]^+$ 363.

5 **Compound 408c:** Compound **407c** (117 mg, 0.3 mmol) was treated according to the procedure for compound **408a** to give the title compound **408c** (117 mg). MS: m/z $[M+H]^+$ 392.

Compound 408d: Compound **407d** (120 mg, 0.32 mmol) was treated according to the procedure for compound **408a** to give the title compound **408d** (110 mg). MS: m/z $[M+H]^+$ 376.

10 **Compound 408e:** Compound **407e** (180 mg, 0.5 mmol) was treated according to the procedure for compound **408a** to give the title compound **408e** (180 mg). MS: m/z $[M+H]^+$ 364.

Compound TX63724: Compound **408a** (0.19 g, 0.52 mmol) was dissolved in 2 mL of DMF at 0 °C. Br₂ (95 mg, 1.1 eq) was added, and the solution was stirred for
15 2 hours. Pyridine (2 mL) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–45% EtOAc/Hexanes to give **TX63724** as an off-white solid (45 mg, 24% yield). ¹H NMR (400 MHz, CDCl₃) δ 9.60 (s, 1H), 8.86 (s, 1H), 8.77 (m, 1H), 8.67 (m, 1H), 7.48 (dd, 1H, J = 4.9, 7.8 Hz), 4.06 (s, 3H), 2.82 (ddd, 1H, J = 1.1, 6.8, 18.7
20 Hz), 2.47-2.64 (m, 2H), 2.03-2.13 (m, 2H), 1.69 (m, 1H), 1.40 (s, 3H), 1.25 (d, 3H, J = 6.7 Hz); MS: m/z $[M+H]^+$ 361.

Compound TX63728: Compound **408b** (0.28 g, 0.77 mmol) was treated according to the procedure for compound **TX63724** to give **TX63728** (25 mg, 9%).
25 ¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 8.46 (bs, 2H), 8.06 (m, 2H), 3.80 (s, 3H), 2.56 (dd, 1H, J = 5.9, 18.9 Hz), 2.22-2.35 (m, 2H), 1.75-1.87 (m, 2H), 1.44 (m, 1H), 1.13 (s, 3H), 0.99 (d, 3H, J = 6.7 Hz); MS: m/z $[M+H]^+$ 361.

Compound TX63727: To a solution of compound **408c** (0.117 g, 0.3 mmol) in 2 mL of DMF at 0 °C was added 1,3-dibromo-5,5-dimethylhydantoin (0.55 eq), and the solution was stirred for 2 hours. Pyridine (1 g) was added, and the solution
30 was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–30% EtOAc/Hexanes to give **45** (80 mg). ¹H NMR (400 MHz, CDCl₃) δ 8.97 (s, 1H), 7.81 (dd, 1H, J = 1.8, 7.6 Hz), 7.42 (m, 1H), 7.04-7.09 (m, 2H), 4.03 (s, 3H), 3.89 (s, 3H), 2.85 (ddd, 1H, J = 1.0, 6.7, 18.5 Hz),

2.51-2.66 (m, 2H), 2.07-2.17 (m, 2H), 1.75 (m, 1H), 1.43 (s, 3H), 1.30 (d, 3H, $J = 6.7$ Hz); MS: m/z $[M+H]^+$ 390.

Compound TX63769: Compound **408d** (110 mg, 0.29 mmol) was treated according to the procedure for compound **TX63727** to give **TX63769** (75 mg, 69%).
5 ^1H NMR (400 MHz, CDCl_3) δ 9.00 (s, 1H), 8.46 (m, 2H), 7.49 (m, 2H), 4.10 (s, 3H), 2.86 (ddd, 1H, $J = 1.0, 6.8, 18.4$ Hz), 2.59 (m, 2H), 2.13 (m, 2H), 1.74 (m, 2H), 1.45 (s, 3H), 1.31 (d, 3H, $J = 6.7$ Hz); MS: m/z $[M+H]^+$ 374.

Compound TX63757: Compound **408e** (180 mg, 0.5 mmol) was treated according to the procedure for compound **TX63724** to give **TX63757** (100 mg).
10 ^1H NMR (400 MHz, CDCl_3) δ 9.70 (s, 2H), 9.33 (s, 1H), 8.89 (s, 1H), 4.13 (s, 3H), 2.90 (ddd, 1H, $J = 0.9, 6.6, 18.8$ Hz), 2.63 (m, 2H), 2.16 (m, 2H), 1.77 (m, 1H), 3.49 (s, 3H), 1.33 (d, 3H, $J = 6.8$ Hz); MS: m/z $[M+H]^+$ 362.

Compound 409: Compound **401b** (515 mg, 1.75 mmol) was dissolved in DMAc (10 mL). To this solution was added $\text{Zn}(\text{CN})_2$ (135 mg, 1.15 mmol), dppf (200
15 mg, 0.36 mmol) and Na_2CO_3 (190 mg, 1.75 mmol). Nitrogen was bubbled through the mixture for 10 min. $\text{Pd}(\text{OAc})_2$ (40 mg, 0.018 mmol) was added and nitrogen bubbled for another 10 min. The suspension was heated to 120 °C for 16 hours. The reaction mixture was quenched with 50 mL of water and extracted with ether (2×50 mL). The organic extracts were concentrated, and purified on a silica gel column, eluted with 5–
20 20% EtOAc/Hexanes to give **409** as an off-white solid (0.2 g, 40% yield). MS (APCI): m/z $[M+H]^+$ 286.

Compound 410: To a solution of **409** (0.2 g, 0.7 mmol) in 10 mL of HCOOEt was added dropwise 30% NaOMe in MeOH (6 eq). The reaction mixture was stirred at RT overnight, then poured into water and acidified with KH_2PO_4 . The mixture was
25 extracted with EtOAc. The combined organic extracts were washed with brine, dried with MgSO_4 , and concentrated in vacuo to give **410** (220 mg). MS: m/z $[M+H]^+$ 361.

Compound 411: To a solution of **410** (0.22 g, 0.7 mmol) in 20 mL of EtOH was added $\text{NH}_2\text{OH} \cdot \text{HCl}$ salt (2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with
30 EtOAc. The combined organic extracts were washed with brine, dried with MgSO_4 , concentrated in vacuo to give **411** (60 mg, 30% yield). MS: m/z $[M+H]^+$ 358.

Compound 412: A solution of **411** (60 mg, 0.17 mmol) and 1 mL of triethylamine in 2 mL of acetonitrile was heated at 85 °C for 16 h. The reaction

mixture was pumped under vacuo to dryness to give **412** (60 mg). MS: m/z $[M+H]^+$ 358.

Compound TX63730: To a solution of compound **412** (60 mg, 0.17 mmol) in 1 mL of DMF at 0 °C was added 1,3-dibromo-5,5-dimethylhydantoin (0.55 eq), and the solution was stirred for 2 hours. Pyridine (1 g) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–30% EtOAc/Hexanes to give **TX63730** (25 mg, 41%). ^1H NMR (400 MHz, CDCl_3) δ 8.83 (s, 1H), 4.42 (m, 2H), 4.03 (s, 3H), 2.82 (m, 1H), 2.45–2.63 (m, 2H), 2.10 (m, 1H), 2.02 (dd, 1H, $J = 2.7, 12.8$ Hz), 1.70 (m, 1H), 1.39 (t, 3H, $J = 7.1$ Hz), 1.37 (s, 3H), 1.25 (d, 3H, $J = 6.7$ Hz); MS: m/z $[M+H]^+$ 356.

Compound 413: A solution of sl. impure **372** (1.39 g, assume 4.20 mmol) and *N,N*-diisopropylethylamine (0.80 mL, 4.60 mmol) in 20 mL of benzene was added dropwise (via syringe) phosphorus oxychloride (4.0 mL, 42.9 mmol). After addition, the sample was heated at 90 °C under N_2 for 4 h, cooled, concentrated then carefully partitioned between EtOAc and sat. NaHCO_3 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give 0.75 g (55%) of **413** as light yellow oil. MS (APCI) m/z 323/325 $[M+H]^+$ (100/91%).

Compound 414a: A solution of **413** (0.44 g, 1.36 mmol), *N,N*-diisopropylethylamine (1.00 mL, 5.74 mmol) and morpholine (0.24 mL, 2.75 mmol) in 10 mL of *i*-PrOH was flushed with N_2 , sealed and heated at 90 °C for 48 h. The sample was cooled, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give 0.50 g (98%) of **414a** as a light tan foamy solid, which was used without purification. MS (APCI): m/z 374 $[M+H]^+$ (100%).

Compound 415a: A solution of **414a** (0.50 g, 1.34 mmol) and 3 N HCl (5 mL, 15 mmol) in 5 mL of MeOH was stirred at room temperature under N_2 for 16 h. The sample was concentrated, cooled, basified with 10% aq. NH_4OH solution to a pH ~ 9–10 and extracted with EtOAc. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give 0.37 g (84%) of **415a** as a tan solid, which was used without purification. MS (APCI) m/z 330 $[M+H]^+$ (100%).

Compound 416a: To a stirring solution of sl. impure **415a** (0.37 g, 1.12 mmol) and ethyl formate (9.0 mL, 111.0 mmol) in 10 mL of benzene was added

dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (1.0 mL, 5.3 mmol). The sample was stirred at room temperature under N₂ for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.45 g (>100%) of sl. impure **416a** as a dark yellow oil, which was used without purification.

Compound 417a: A solution of sl. impure **416a** (0.45 g, assume 1.12 mmol) and hydroxylamine hydrochloride (0.12 g, 1.73 mmol) in 20 mL of EtOH was heated at 50 °C under N₂ for 2 h, cooled, concentrated and partitioned between CHCl₃ and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.47 g (100%) of a dark yellow oil, which by TLC and MS was a mixture of desired **417a** and undehydrated product. TLC (silica gel, 50% EtOAc/Hexanes) 2 components; R_f = 0.47 and 0.12. MS (ES) *m/z* 355 (100%) [M+H]⁺. A solution of the above mixture (entire amount) and a pinch of *p*-toluenesulfonic acid monohydrate in 50 mL of benzene were heated at 90 °C under N₂ for 2 h (TLC showed no lower component remaining). The sample was cooled and concentrated to give 0.77 g (>>100%) of **417a** as a dark yellow oil, which was used without purification.

Compound 418a: To a stirring solution of sl. impure **417a** (entire amount of crude mixture from previous step, assume 1.12 mmol) at room temperature under N₂ in 10 mL of MeOH was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (1.1 mL, 5.9 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.37 g (94%) of **418a** as a yellow solid, which was used without purification.

Compound TX63758: To a stirring solution at 0 °C under N₂ of sl. impure **418a** (0.37 g, 1.05 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.15 g, 0.52 mmol). After stirring at 0 °C for 1 h, pyridine (1.0 mL, 12 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 40% EtOAc/Hexanes) to give 0.20 g (54%) of **TX63758** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.84 (s, 1H), 3.84 (ddd, 2H, *J* =

2.9, 6.4, 11.3 Hz), 3.75 (ddd, 2H, $J = 2.8, 6.6, 11.2$ Hz), 3.43 (ddd, 2H, $J = 2.4, 6.4, 13.1$ Hz), 3.22 (ddd, 2H, $J = 2.4, 6.5, 13.1$ Hz), 2.68 (m, 2H), 2.55 (m, 1H), 2.55 (s, 3H), 2.11 (m, 2H), 1.69 (m, 1H), 1.39 (s, 3H), 1.29 (d, 3H, $J = 6.7$ Hz); MS (APCI) m/z 353 $[M+H]^+$ (100%).

5 **Compound 414b:** A mixture of **413** (0.38 g, 1.17 mmol), *N,N*-diisopropylethylamine (0.72 mL, 4.13 mmol) and dimethylamine hydrochloride (0.11 g, 1.35 mmol) in 10 mL of *n*-BuOH was flushed with N_2 , sealed and heated at 90 °C for 16 h. The sample was cooled, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried
10 (MgSO₄), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give 0.25 g (64%) of **414b** as a white waxy solid. MS (APCI) m/z 332 $[M+H]^+$ (100%).

Compound 415b: A solution of **414b** (0.25 g, 0.75 mmol) and 3N HCl (6 mL, 18 mmol) in 10 mL of MeOH was stirred at room temperature under N_2 for 16 h. The
15 sample was concentrated, cooled, basified with 10% aq. NH_4OH solution to a pH ~9–10 and extracted with EtOAc. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.22 g (>100%) of sl. impure **415b** as a light yellow oil, which was used without purification.

Compound 416b: To a stirring solution of sl. impure **415b** (entire amount
20 from previous step, assume 0.75 mmol) and ethyl formate (6.1 mL, 75.5 mmol) in 10 mL of benzene was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (1.42 mL, 7.57 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated then partitioned between $CHCl_3$ and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and
25 concentrated to give 0.25 g (>100%) of sl. impure **416b** as a yellow oil, which was used without purification.

Compound 417b: A solution of sl. impure **416b** (entire amount from previous step, assume 0.75 mmol) and hydroxylamine hydrochloride (0.080 g, 1.15 mmol) in 10 mL of EtOH was heated at 50 °C under N_2 for 2 h, then room temperature
30 overnight. The sample was concentrated and partitioned between $CHCl_3$ and sat. $NaHCO_3$ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.23 g (98%) of a yellow oil, which by TLC and MS was a mixture of desired **417b** and undehydrated product. TLC (silica gel, 40% EtOAc/Hexanes) 2 components; $R_f = 0.38$ and 0.06. MS (APCI) m/z 331

(M+19, 70%) and 313 (M+1, 100%). A solution of the above mixture (entire amount) and a pinch of *p*-toluenesulfonic acid monohydrate in 50 mL of benzene were heated at 90 °C under N₂ for 2 h (TLC showed no lower component remaining). The sample was cooled and concentrated and partitioned between CHCl₃ and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.20 g (83%) **417b** as a light yellow foamy solid, which was used without purification.

Compound 418b: To a stirring solution of sl. impure **417b** (0.20 g, 0.63 mmol) at room temperature under N₂ in 10 mL of MeOH was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (1.2 mL, 6.4 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between CHCl₃ and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.20 g (99%) of sl. impure **418b** as a dark yellow oil, which was used without purification.

Compound TX63774: To a stirring solution at 0 °C under N₂ of sl. impure **418b** (0.20 g, 0.62 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.088 g, 0.31 mmol). After stirring at 0 °C for 1 h, pyridine (0.50 mL, 6.18 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between CHCl₃ and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give 0.046 g (24%) of **TX63774** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.85 (s, 1H), 3.00 (s, 6H), 2.75 (m, 2H), 2.54 (m, 1H), 2.52 (s, 3H), 2.10 (m, 2H), 1.67 (s, 1H), 1.39 (s, 3H), 1.29 (d, 3H, *J* = 6.7 Hz); MS (APCI) *m/z* 311 [M+H]⁺ (100%).

Compound 414c: A mixture of **413** (0.44 g, 1.37 mmol), *N,N*-diisopropylethylamine (0.26 mL, 1.49 mmol) and *n*-butylamine (0.70 mL, 7.08 mmol) in 5 mL of *n*-BuOH was flushed with N₂, sealed and heated at 90 °C for 48 h. The sample was cooled, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.59 g (>100%) of sl. impure **414c** as a yellow oil, which was used without purification. MS (APCI) *m/z* 360 [M+H]⁺ (100%).

Compound 415c: A solution of sl. impure **414c** (entire amount from previous step, assume 1.37 mmol) and 3N HCl (5 mL, 15 mmol) in 10 mL of MeOH was stirred at room temperature under N₂ for 16 h. The sample was concentrated, cooled, basified with 10% aq. NH₄OH solution to a pH ~ 9–10 and extracted with CHCl₃.
5 The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.42 g (98%) of sl. impure **415c** as a light yellow oil, which was used without purification. MS (APCI) *m/z* 316 [M+H]⁺ (100%).

Compound 416c: To a stirring solution of sl. impure **415c** (0.42 g, 1.34 mmol) and ethyl formate (10.8 mL, 133.7 mmol) in 20 mL of benzene was added
10 dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (1.25 mL, 6.66 mmol). The sample was stirred at room temperature under N₂ for 16 h, concentrated then partitioned between CHCl₃ and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.60 g (>100%) of sl. impure **416c** as a dark yellow oil, which was used without
15 purification. MS (APCI) *m/z* 344 [M+H]⁺ (100%).

Compound 417c: A solution of sl. impure **416c** (entire amount from previous step, assume 1.34 mmol) and hydroxylamine hydrochloride (0.24 g, 3.45 mmol) in 10 mL of EtOH was heated at 50 °C under N₂ for 2 h, then room temperature overnight. The sample was concentrated and partitioned between CHCl₃ and sat. NaHCO₃
20 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.58 g (>100%) of a dark yellow oil, which by TLC and MS was a mixture of desired **417c** and undehydrated product. TLC (silica gel, 50% EtOAc/Hexanes) 2 components; R_f = 0.42 and 0.06. MS (APCI) *m/z* 359 (M+19, 70%) and 341 (M+1, 100%). A solution of the above mixture (entire amount)
25 and a pinch of *p*-toluenesulfonic acid monohydrate in 50 mL of benzene was heated at 90 °C under N₂ for 2 h (TLC showed no lower component remaining). The sample was cooled and concentrated and partitioned between CHCl₃ and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.46 g (~100%) of **417c** as a dark yellow oil, which
30 was used without purification. (APCI) *m/z* 341 [M+H]⁺ (100%).

Compound 418c: To a stirring solution of sl. impure **417c** (0.46 g, assume 1.34 mmol) at room temperature under N₂ in 10 mL of MeOH was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (1.25 mL, 6.66 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between

CHCl₃ and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 50% EtOAc/Hexanes) to give 0.19 g (41%) of **418c** as yellow oil.

Compound TX63827: To a stirring solution at 0 °C under N₂ of **418c** (0.19 g, 0.55 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.078 g, 0.27 mmol). After stirring at 0 °C for 1 h, pyridine (0.44 mL, 5.44 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 50% EtOAc/Hexanes) to give 0.079 g (43%) of **TX63827** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.91 (s, 1H), 4.39 (s, br, 1H), 3.49 (q, 1H, *J* = 7.2 Hz), 2.45-2.54 (m, 1H), 2.48 (s, 3H), 2.28-2.44 (m, 2H), 2.08-2.17 (m, 1H), 2.01 (dt, 1H, *J* = 2.4, 12.8 Hz), 1.68-1.81 (m, 1H), 1.50-1.62 (m, 3H), 1.31-1.45 (m, 2H), 1.37 (s, 3H), 1.26 (d, 3H, *J* = 6.8 Hz), 0.94 (t, 3H, *J* = 7.6 Hz); MS (APCI) *m/z* 339 (100%) [M+H]⁺.

Compound 414d: A mixture of **413** (0.40 g, 1.24 mmol) and methylamine, 2.0 M solution in THF (3.1 mL, 12.4 mmol) in 10 mL of *i*-PrOH was flushed with N₂, sealed and heated at 90 °C for 48 h. The sample was cooled, concentrated then partitioned between CHCl₃ and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 100% EtOAc) to give 0.34 g (87%) of **414d** as a white solid. MS (APCI) *m/z* 318 [M+H]⁺ (100%).

Compound 415d: A solution of **414d** (0.34 g, 1.08 mmol) and 3N HCl (6 mL, 18 mmol) in 12 mL of MeOH:THF (2:1) was stirred at room temperature under N₂ for 16 h. The sample was concentrated, cooled, basified with 10% aq. NH₄OH solution to a pH ~ 9–10 and extracted with CHCl₃. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.26 g (87%) of sl. impure **415d** as a light yellow foamy solid, which was used without purification.

Compound 416d: To a stirring solution of sl. impure **415d** (0.26 g, 0.94 mmol) and ethyl formate (7.6 mL, 94.1 mmol) in 10 mL of benzene was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (0.88 mL, 4.69 mmol). The sample was stirred at room temperature under N₂ for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was

washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.20 g (70%) of sl. impure **416d** as a light yellow solid, which was used without purification. MS (APCI) *m/z* 302 [M+H]⁺ (100%).

Compound 417d: A solution of sl. impure **416d** (0.20 g, 0.65 mmol) and hydroxylamine hydrochloride (0.069 g, 0.99 mmol) in 10 mL of EtOH was heated at 50 °C under N₂ for 2 h, then room temperature overnight. The sample was concentrated and partitioned between CHCl₃ and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.24 g (>100%) of a yellow foamy solid, which by TLC and MS was a mixture of desired **417d** and undehydrated product. TLC (silica gel, 5% MeOH/CHCl₃) 2 components; R_f = 0.44 and 0.13. MS (APCI) *m/z* 317 (M+19, 52%) and 299 (M+1, 100%). A solution of the above mixture (entire amount) and a pinch of *p*-toluenesulfonic acid monohydrate in 50 mL of benzene was heated at 90 °C under N₂ for 4 h (TLC showed no lower component remaining). The sample was cooled and concentrated and partitioned between CHCl₃ and 10% aq. NH₄OH solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.20 g (>100%) of sl. impure **417d** as a yellow solid, which was used without purification. MS (APCI) *m/z* 299 [M+H]⁺ (100%).

Compound 418d: To a stirring solution of sl. impure **417d** (0.20 g, assume 0.65 mmol) at room temperature under N₂ in 10 mL of MeOH was added dropwise (via syringe) NaOMe, 30 wt% solution in MeOH (0.61 mL, 3.25 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between CHCl₃ and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give 0.17 g (89%) of **418d** as a light yellow solid, which was used without purification.

Compound TX63852: To a stirring solution at 0 °C under N₂ of **418d** (0.17 g, 0.58 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.083 g, 0.29 mmol). After stirring at 0 °C for 1 h, pyridine (0.47 mL, 5.81 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 75% EtOAc/Hexanes) to give 0.044 g (25%) of **TX63852** as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.93 (s, 1H), 4.48 (s,

br, 1H), 3.05 (d, 3H, $J = 4.4$ Hz), 2.29-2.57 (m, 3H), 2.51 (s, 3H), 2.09-2.13 (m, 1H), 2.03 (t, 1H, $J = 13.2$ Hz), 1.68-1.82 (m, 1H), 1.37 (s, 3H), 1.28 (d, 3H, $J = 6.8$ Hz); MS (APCI) m/z 297 $[M+H]^+$ (100%).

Compound 419a-b: A solution of **400** (0.56 g, 1.87 mmol) and Na metal (200 mg, 8.7 mmol) in 15 mL of EtOH was heated at 50 °C for 3 h. The reaction mixture was concentrated, extracted with EtOAc (2× 25 mL), washed with water, and purified on a silica gel column. Two compounds were isolated with 10–15% EtOAc/Hexanes elution. The first compound was **419a** (160 mg, 28% yield), MS: m/z $[M+H]^+$ 309, 311 (3:1). The second compound was **419b** (210 mg, 35% yield). MS: m/z $[M+H]^+$ 319.

Compound 420: To a solution of **419b** (210 mg, 0.66 mmol) in 5 mL of HCOOEt at RT, a solution of Na metal (50 mg, 2.17 mmol) in EtOH (5 mL) was added dropwise. The reaction mixture was stirred at RT overnight, poured into water and acidified with KH_2PO_4 . The mixture was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **420** (210 mg, 92% yield). MS: m/z $[M+H]^+$ 347.

Compound 421: To a solution of **420** (0.21 g, 0.6 mmol) in 13 mL of EtOH was added $NH_2OH \cdot HCl$ salt (2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **421** (210 mg). MS: m/z $[M+H]^+$ 344.

Compound 422: To a solution of **421** (0.21 g, 0.6 mmol) in 3 mL of THF and 1.5 mL of MeOH was added dropwise 30% NaOMe (8 eq), and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with sat. KH_2PO_4 (20 mL) and extracted with EtOAc. The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **422** (200 mg). MS: m/z $[M+H]^+$ 344.

Compound TX63736: To a solution of **422** (200 mg, 0.58 mmol) in 2 mL of DMF at 0 °C was added 1,3-dibromo-5,5-dimethylhydantoin (0.55 eq), and the solution was stirred for 2 hours. Pyridine (1 g) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–30% EtOAc/Hexanes to give **TX63736** as an off-white solid (23 mg, 12%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 4.44 (t, 2H, $J = 7.1$), 4.42 (t, 2H, $J = 7.0$), 2.74 (ddd, 1H, $J = 0.9, 6.7, 17.9$ Hz), 2.51 (m, 2H), 2.08 (m,

2H), 1.69 (m, 1H), 1.45 (t, 3H, $J = 7.1$ Hz), 1.40 (s, 3H), 1.39 (t, 3H, $J = 7.1$ Hz), 1.30 (d, 3H, $J = 6.8$ Hz); MS: m/z $[M+H]^+$ 342.

Compound 423: Compound **419a** (0.16 g, 0.51 mmol) was dissolved in DME (6 mL) and DMF (3 mL). To this solution was added phenylboronic acid (80 mg, 0.65 mmol), Ph_3P (85 mg, 0.32 mmol) and K_3PO_4 (0.33 g, 1.56 mmol). Nitrogen was bubbled through the mixture for 10 min. $Pd(OAc)_2$ (35 mg, 0.16 mmol) was added and nitrogen bubbled for another 10 min. The suspension was heated to 90 °C for 16 hours. The reaction mixture was filtered, concentrated, and purified on a silica gel column, eluted with 5–25% EtOAc/Hexanes to give **423** as a solid (120 mg, 67% yield). MS: m/z $[M+H]^+$ 351.

Compound 424: To a solution of **423** (120 mg, 0.34 mmol) in 2.5 mL of HCOOEt was added dropwise 30% NaOMe in MeOH (6 eq). The reaction mixture was stirred at RT overnight, then poured into water and acidified with KH_2PO_4 . The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo to give **424** (130 mg). MS: m/z $[M+H]^+$ 379.

Compound 425: To a solution of **424** (130 mg, 0.34 mmol) in 6.5 mL of EtOH was added $NH_2OH \cdot HCl$ salt (2 eq), and the mixture was heated at 50 °C overnight. After concentration in vacuo, the residue was mixed with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **425** (120 mg). MS: m/z $[M+H]^+$ 376.

Compound 426: To a solution of **425** (120 mg, 0.32 mmol) in 1.5 mL of THF and 0.75 mL of MeOH was added dropwise 30% NaOMe (8 eq), and the solution was heated at 50 °C for 6 hours. After concentration in vacuo, the residue was mixed with sat. KH_2PO_4 (20 mL) and extracted with EtOAc. The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated in vacuo to give **426** (110 mg). MS: m/z $[M+H]^+$ 376.

Compound TX63731: To a solution of **426** (110 mg, 0.29 mmol) in 2 mL of DMF at 0 °C was added 1,3-dibromo-5,5-dimethylhydantoin (0.55 eq), and the solution was stirred for 2 hours. Pyridine (1 g) was added, and the solution was heated at 50 °C overnight. After concentration in vacuo, the residue was purified on a silica gel column, eluted with 5–30% EtOAc/Hexanes to give **TX63731** (75 mg, 69%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.46 (m, 2H), 7.50 (m, 3H), 4.60 (q, 2H, $J =$

7.1 Hz), 2.87 (ddd, 1H, $J = 1.1, 6.8, 18.6$), 2.61 (m, 2H), 2.14 (m, 2H), 1.76 (m, 1H), 1.46 (s, 3H), 1.46 (t, 3H, $J = 7.1$ Hz), 1.32 (d, 3H, $J = 6.8$ Hz);

MS: m/z $[M+H]^+$ 374.

Compound 427: A solution of **413** (0.38 g, 1.17 mmol) in 20 mL of EtOH was added (dropwise, via syringe) sodium ethoxide, 21 wt% solution in EtOH (4.4 mL, 11.8 mmol). The sample was stirred at room temperature under N_2 for 16 h (TLC, silica gel, 30% EtOAc/Hexanes still showed unreacted starting material) then heated at 70 °C for 8 h. The sample was concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give 0.52 g (>100%) of sl. impure **427** as a dark yellow oil, which was used without purification.

Compound 428: A solution of sl. impure **427** (0.52 g, assume 1.17 mmol) and 3N HCl (4 mL, 12 mmol) in 10 mL of MeOH was stirred at room temperature under N_2 for 16 h. The sample was concentrated, cooled, basified with 10% aq. NH_4OH solution to a pH ~ 9–10 and extracted with EtOAc. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give 0.28 g (84%) of **428** as a tan solid.

Compound 429: To a stirring solution of **428** (0.28 g, 0.98 mmol) and ethyl formate (9.0 mL, 111.0 mmol) in 10 mL of benzene was added dropwise (via syringe) sodium ethoxide, 21 wt% solution in EtOH (3.7 mL, 9.9 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give 0.30 g (96%) of sl. impure **429** as a dark yellow oily solid, which was used without purification.

Compound 430: A solution of **429** (0.30 g, 0.94 mmol) and hydroxylamine hydrochloride (0.10 g, 1.44 mmol) in 10 mL of EtOH was heated at 50 °C under N_2 for 2 h, then room temperature overnight. The sample was concentrated and partitioned between EtOAc and sat. $NaHCO_3$ solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give 0.30 g (>100%) of sl. impure **430** as a tan foamy solid, which was used without purification.

Compound 431: To a stirring solution of sl. impure **430** (entire amount from previous step, assume 0.94 mmol) at room temperature under N_2 in 10 mL of MeOH

was added dropwise (via syringe) sodium ethoxide, 21 wt% solution in EtOH (3.5 mL, 9.4 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give 0.28 g (95%) of sl. impure **431** as a yellow-orange solid, which was used without purification.

Compound TX63773: To a stirring solution at 0 °C under N_2 of sl. impure **431** (0.28 g, 0.89 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.13 g, 0.45 mmol). After stirring at 0 °C for 1 h, pyridine (0.70 mL, 8.65 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give 0.14 g (48%) of **TX63773** as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.87 (s, 1H), 4.40 (q, 2H, J = 7.1 Hz), 2.75 (dd, 1H, J = 7.0, 18.5 Hz), 2.54 (s, 3H), 2.52 (m, 2H), 2.03 (m, 2H), 1.65 (m, 1H), 1.38 (s, 3H), 1.37 (t, 3H, J = 7.1 Hz), 1.27 (d, 3H, J = 6.7 Hz); MS (APCI) m/z 312 $[\text{M}+\text{H}]^+$ (100%).

Compound 432: Compound **127** (0.964 g, 4.04 mmol) was taken up in DCM (100 mL) and $\text{MgBr}_2\cdot\text{Et}_2\text{O}$ (2.707 g, 10.5 mmol) and *i*- Pr_2NEt (1.39 mL, 8.0 mmol) were added. The reaction mixture was stirred at room temperature for about 30 min during which the reaction mixture gradually turned orange. Then, benzoyl chloride (1.17 g, 8.3 mmol) in DCM (3 mL) was added dropwise and the mixture was stirred overnight at room temperature. The reaction was warmed to reflux and the orange color gradually discharged. The reaction was quenched by adding saturated aqueous sodium bicarbonate solution (100 mL) which was stirred for 1 h at room temperature. The organic layer was separated and dried over MgSO_4 , filtered and concentrated to an oil. The oil was chromatographed on silica gel (230–400 mesh, 42 g) 10% EtOAc/Hexanes as eluant to yield the product **432** as an almost clear oil (0.372 g, 27%). MS: m/z $[\text{M}+\text{H}]^+$ 343.1.

Compound 433: Compound **432** (0.372 g, 1.09 mmol) was taken up in EtOH (40 mL) and hydrazine monohydrate (0.244 g, 3.8 mmol) was added. The reaction mixture was heated to 65 °C for 1 h and then stirred at room temperature for 5 d. The reaction mixture was concentrated to dryness and the residual volatiles were removed

under vacuum to give the product **433** as an oil/solid (0.41 g) that was used directly in the next step. MS: m/z $[M+H]^+$ 339.1.

Compound 434: Compound **433** (0.41 g, 1.2 mmol) was taken up in MeOH (35 mL) and 1N HCl (3 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to remove MeOH and was then partitioned between EtOAc (60 mL) and saturated aqueous sodium bicarbonate. The organic layer was dried over MgSO₄, filtered, and concentrated to give **434** as an oil/glass (0.3266 g). m/z $[M+H]^+$ 295.1.

Compound 435: Compound **434** (0.3266 g, 1.11 mmol) was taken up in ethyl formate (50 mL) and 30% NaOMe in MeOH (1.8 mL, 9.7 mmol) was added. The mixture was stirred overnight at room temperature and was then poured into a separatory funnel containing saturated aqueous KH₂PO₄ (20 mL) and EtOAc (125 mL). The organic layer was separated and dried over MgSO₄, filtered and concentrated to an oil/glass that contained a large amount of starting material, and was resubjected to ethyl formate (30 mL) and 30% NaOMe in MeOH (1.2 mL, 6.48 mmol) overnight at room temperature. The reaction was worked up as before to give the product **435** as a yellow glass (0.247g, 70% over three steps). MS: m/z $[M+H]^+$ 323.1.

Compound 436: A solution of 0.1 M hydroxylamine hydrochloride in 9:1 EtOH/water (12 mL, 1.2 mmol) was added to **435** (0.247 g, 0.77 mmol) and the mixture was stirred overnight at room temperature. The following morning the mixture was heated to 50 °C on the rotary evaporator and concentrated to dryness. The crude residue was partitioned between EtOAc (100 mL) and saturated aqueous sodium bicarbonate solution (15 mL) and the organic layer was dried over MgSO₄, filtered and concentrated to a glass. The glass was chromatographed on silica gel (230–400 mesh, 8 g) using 50% EtOAc/Hexanes as eluant to give the product **436** as a glass (0.0844 g, 34%). MS: m/z $[M+H]^+$ 320.1.

Compound 437: Isoxazole **436** (0.0844 g, 0.26 mmol) was taken up in 1:1 MeOH/THF, (10 mL) and 30% NaOMe in MeOH (0.2 mL, 1.08 mmol) was added. The mixture was stirred overnight at room temperature and was then partitioned between saturated KH₂PO₄ (15 mL) and EtOAc (100 mL). The organic layer was separated and dried over MgSO₄, filtered and concentrated to give the product **437** as a glass (0.085 g). MS: m/z $[M+H]^+$ 320.1.

Compound TX63836: Cyanoketone **437** (0.085 g, 0.26 mmol) was taken up in DMF (2.5 mL) and the mixture was cooled to 0°C. Dibromodimethylhydantoin (0.048 g, 0.17 mmol) was added and the reaction was stirred for 1.75 h. Anhydrous pyridine (0.25 mL, 3.1 mmol) was added and the reaction mixture was heated at 60 °C for 3 h. The reaction mixture was concentrated to dryness and chromatographed on silica gel (230-400 mesh, 6 g) using 3:1 Hexanes/EtOAc as eluant to give the product **TX63836** as an off-white solid (0.0355 g, 43% over two steps). ¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H), 7.42-7.50 (m, 5H), 7.33-7.41 (m, 1H), 2.91 (dd, 1H, *J* = 6.4, 16.4 Hz), 2.70-2.82 (m, 1H), 2.51-2.62 (m, 1H), 2.05-2.18 (m, 2H), 1.69-1.85 (m, 1H), 1.46 (s, 3H), 1.31 (d, 3H, *J* = 6.8 Hz); MS: *m/z* [M+H]⁺ 318.0.

Compound TX63850: Compound **TX63836** (0.015 g, 0.047 mmol) was mixed with Ac₂O (2 mL) and anhydrous NaOAc (0.013 g, 0.16 mmol). The mixture was stirred for 3 days at room temperature and was then concentrated to dryness and filtered through silica gel (230-400 mesh, 1 g) using 4:1 Hexanes/EtOAc to give the product **TX63850** as a glass (0.0052 g, 31%). ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H), 7.28-7.41 (m, 3H), 7.15-7.27 (m, 2H), 2.63 (s, 3H), 2.38-2.62 (m, 4H), 1.90-2.10 (m, 2H), 1.43 (s, 3H), 1.23 (d, 3H, *J* = 6.4 Hz); MS: *m/z* [M+H]⁺ 360.1.

Compound TX63871: Compound **TX63836** (0.015 g, 0.047 mmol) was mixed with ethylchloroformate (1 mL) and solid NaHCO₃ (0.056 g, 6.67 mmol) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to dryness and chromatographed on silica gel (230-400 mesh, 4 g) using 3:1 Hexanes/EtOAc to give the product **TX63871** as an off-white solid (0.014 g, 76%). ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 7.65-7.70 (m, 2H), 7.36-7.45 (m, 3H), 4.57 (q, 2H, *J* = 7.2 Hz), 2.69-2.81 (m, 2H), 2.59-2.68 (m, 1H), 2.18 (dd, 1H, *J* = 1.2, 12.4 Hz), 2.02-2.10 (m, 1H), 1.62-1.74 (m, 1H), 1.67 (s, 3H), 1.51 (t, 3H, *J* = 6.8 Hz), 1.34 (d, 3H, *J* = 6.8 Hz); MS: *m/z* [M+H]⁺ 390.1.

Compound 438: Compound **127** (0.971 g, 4.1 mmol) was taken up in DCM (50 mL) and MgBr₂·Et₂O (2.90 g, 11.2 mmol) and *i*-Pr₂NEt (2.4 mL, 13.8 mmol) were added. The reaction mixture was stirred at room temperature for about 30 min, during which time the mixture gradually turned orange. Pyridine-2-carboxylic acid chloride hydrochloride (1.71 g, 9.6 mmol) was added and the mixture was stirred overnight at room temperature. The reaction was quenched by adding excess saturated aqueous sodium bicarbonate solution. The very dark reaction mixture was concentrated to remove DCM and EtOAc (250 mL) and excess saturated KH₂PO₄

were added. The organic layer was separated, dried over MgSO_4 , and concentrated to give **438** as dark oil (1.09 g) that was used directly in the next step. MS: m/z $[\text{M}+\text{H}]^+$ 344.1.

Compound 439: Crude **438** (1.09 g, 3.2 mmol) was taken up in EtOH (100 mL) and methylhydrazine (1.306 g, 28.4 mmol) was added. The reaction mixture was stirred overnight at room temperature and then heated to 70 °C, after which more EtOH was added and heating was continued at 70 °C. The reaction mixture was concentrated to dryness and the dark oil was chromatographed on silica gel (230–400 mesh, 40 g) using 50% Hexanes/EtOAc and then EtOAc as eluant to give the product **439** as a yellow oil/glass (0.1453 g, 10% over two steps). MS: m/z $[\text{M}+\text{H}]^+$ 354.2.

Compound 440: Compound **439** (0.1453 g, 0.41 mmol) was taken up in MeOH (25 mL) and 1N HCl (4 mL) and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated to remove MeOH and was then partitioned between EtOAc (100 mL) and saturated aqueous sodium bicarbonate. The organic layer was dried over MgSO_4 , filtered and concentrated to give **440** as oil/glass (0.1197 g, 94%). m/z $[\text{M}+\text{H}]^+$ 310.1.

Compound 441: Compound **440** (0.1197 g, 0.39 mmol) was taken up in ethyl formate (20 mL) and 30% NaOMe in MeOH (0.6 mL, 3.24 mmol) was added. The mixture was stirred 3 d at room temperature and was then poured into a separatory funnel containing saturated aqueous KH_2PO_4 (20 mL) and EtOAc (100 mL). The organic layer was separated and dried over MgSO_4 , filtered and concentrated to give **441** as an orange glass (0.1267 g, 96%). MS: m/z $[\text{M}+\text{H}]^+$ 338.1.

Compound 442: A solution of 0.1 M hydroxylamine hydrochloride in 9:1 EtOH/water (6 mL, 0.6 mmol) was added to **441** (0.1267 g, 0.37 mmol) and the mixture was stirred overnight at room temperature. Upon completion the mixture was concentrated to dryness ($T = 50$ °C) and the residue was partitioned between EtOAc (100 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The organic solution was dried over MgSO_4 , filtered and concentrated to give **442** as a yellow glass (0.1053 g, 85%). MS: m/z $[\text{M}+\text{H}]^+$ 335.1.

Compound 443: Compound **442** (0.1053 g, 0.31 mmol) was taken up in 1:1 MeOH/THF (10 mL) and 30% NaOMe in MeOH (0.25 mL, 1.35 mmol) was added. The mixture was stirred overnight at room temperature and was then partitioned between saturated KH_2PO_4 (15 mL) and EtOAc (100 mL). The organic layer was

separated, dried over MgSO_4 , filtered and concentrated to give the product **443** as a glass (0.1022 g, 99%). MS: m/z $[\text{M}+\text{H}]^+$ 335.1.

Compound TX63851: Compound **443** (0.1022 g, 0.31 mmol) was taken up in DMF (2.5 mL) and the mixture was cooled to 0 °C. Br_2 (0.055 g, 0.34 mmol) in DMF (0.3 mL) was added and the reaction was stirred for 1.75 h. Anhydrous pyridine (0.25 mL, 3.1 mmol) was added and the reaction mixture was heated at 60 °C for 3 h. The reaction mixture was concentrated to dryness and partitioned between EtOAc (80 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The organic layer was washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated to a brown oil/glass. The oil was chromatographed on silica gel (230–400 mesh, 8 g) using 50% Hexanes/EtOAc as eluant and rechromatographed on silica gel (230–400 mesh, 6 g) using 50% Hexanes/EtOAc as eluant to give the product **TX63851** (0.0163 g, 16%). ^1H NMR (400 MHz, CDCl_3) δ 8.65 (d, 1H, J = 4.4 Hz), 8.44 (s, 1H), 7.72 (t, 1H, J = 7.6 Hz), 7.32 (d, 1H, J = 7.6 Hz), 7.17–7.24 (m, 1H), 3.98 (s, 3H), 2.55–2.75 (m, 2H), 2.44–2.55 (m, 1H), 1.94–2.11 (m, 2H), 1.62–1.75 (m, 1H), 1.38 (s, 3H), 1.24 (d, 3H, J = 6.8 Hz); MS: m/z $[\text{M}+\text{H}]^+$ 333.1.

Compound TX63849: Compound **TX63690** (0.034 g, 0.10 mmol) was taken up in acetonitrile (1 mL) and Accufluor (0.042 g, 0.126 mmol (based on 3 mmol/g)) was added. The mixture was stirred 2 h at 80 °C and then 3 d at room temperature. More Accufluor (0.046 g, 0.138 mmol) was added and the mixture was heated overnight at 80 °C. The reaction mixture was concentrated and chromatographed on silica gel (230–400 mesh, 6 g) using EtOAc and then 5% THF/EtOAc as eluant. The product-containing fractions were chromatographed again on silica gel (230–400 mesh, 2.8 g) using 1.2% MeOH /DCM as eluant to give the product **TX63849** (0.005 g, 14%). ^1H NMR (400 MHz, CDCl_3) δ 8.29 (s, 1H), 7.28 (s, 1H), 7.27 (s, 1H), 3.87 (s, 3H), 3.32 (s, 3H), 2.72 (d, 1H, J = 14.0 Hz), 2.40–2.51 (m, 1H), 1.45–1.96 (m, 4H), 1.22 (d, 3H, J = 6.8 Hz), 1.12 (s, 3H); MS: m/z $[\text{M}+\text{H}]^+$ 352.1.

Compound 444 and 445: A solution of **181** (1.663 g, 5.223 mmol) and Et_3N (1.0 mL, 5.94 mmol) in CHCl_3 (50 mL) under N_2 was cooled to 0 °C and methyl trifluoromethanesulfonate (1.0 mL, 8.8 mmol) was added dropwise. The solution was allowed to warm to room temperature overnight then washed with sat. NaHCO_3 and sat. NaCl solutions, dried (MgSO_4), filtered and concentrated. Chromatography (silica gel, 70% EtOAc /Hexanes) afforded **444** (0.786 g, 33%) as an off-white solid;

MS (APCI) m/z 333 ($M+1$, 100); and **445** (0.247 g, 10%) as a light yellow oil; MS (APCI) m/z 333 (100) $[M+H]^+$.

Compound 446: A solution of **444** (0.786 g, 2.365 mmol) and 3N HCl (4 mL, 12 mmol) in 20 mL of MeOH:THF (1:1) was stirred at room temperature under N_2 for 16 h. The solution was concentrated then partitioned between $CHCl_3$ and 10% aq. NH_4OH . The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **446** (0.633 g, 93%) as foamy white solid. MS (APCI) m/z 289 (100%) $[M+H]^+$.

Compound 447: To a solution of **446** (1.8 mL, 22.3 mmol) in benzene (10 mL) was added dropwise (via syringe) NaOMe (30 wt% in MeOH, 2.0 mL, 10.7 mmol) under N_2 . The sample was stirred at room temperature for 16 h, concentrated, and then partitioned between EtOAc and sat. $NaHCO_3$ solution. The organic extract was washed with sat. KH_2PO_4 and sat. NaCl solutions, dried ($MgSO_4$), filtered and concentrated to give **447** (0.502 g, 72%) as a light brown foamy solid. MS (APCI) m/z 317 (100%) $[M+H]^+$.

Compound 448: A solution of **447** (0.502 g, assume 1.585 mmol) in ethanol (10 mL) was treated with solid hydroxylamine hydrochloride (0.16 g, 2.30 mmol). The sample was heated at 50 °C under N_2 for 2 h and then room temperature overnight. The sample was concentrated then partitioned between $CHCl_3$ and sat. $NaHCO_3$ solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **448** (0.658 g, >100%) as a light brown foamy solid. MS (APCI) m/z 314 (100%) $[M+H]^+$.

Compound 449: A solution of slightly impure **448** (0.658 g, assume 1.585 mmol) in MeOH (10 mL) was treated with NaOMe (30 wt% in MeOH, 1.48 mL, 7.89 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solutions, dried ($MgSO_4$), filtered and concentrated to give **449** (0.578 g, >100%) as a yellow foamy solid. MS (APCI) m/z 314 (100%) $[M+H]^+$.

Compound TX63584: Dibromodimethylhydantoin (0.272 g, 0.951 mmol) was added to a stirring solution of slightly impure **449** (0.578 g, assume 1.585 mmol) in DMF (10 mL) at 0 °C under N_2 . After stirring at 0 °C for 1 h, pyridine (1.3 mL, 16.1 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 16 h. The sample was concentrated (to remove most of the DMF and pyridine) and then partitioned between EtOAc and sat. $NaHCO_3$ solution. The organic extract

was washed with sat. KH_2PO_4 and sat. NaCl solution, dried (MgSO_4), filtered, and concentrated. Purification by chromatography (silica gel, 2% MeOH/ CHCl_3) afforded **TX63584** (0.151 g, 31%) as light yellow foamy solid. ^1H NMR (500 MHz, CDCl_3) δ 8.75 (s, 1H), 3.51 (s, 3H), 2.79 (dd, 1H, $J = 6.1, 18.5$ Hz), 2.57 (s, 3H), 2.46 (dddd, 1H, $J = 7.4, 9.4, 9.4, 11.4$ Hz), 2.06 (dd, 1H, $J = 2.0, 12.8$ Hz), 1.96 (dd, 1H, $J = 7.3, 13.3$ Hz), 1.76 (m, 1H), 1.42 (s, 3H), 1.26 (s, 3H), 1.20 (s, 3H); MS (APCI) m/z 312 (100%) $[\text{M}+\text{H}]^+$.

Compound 450: A solution of **445** (0.247 g, 0.742 mmol) and 3 N HCl (4 mL, 12 mmol) in 20 mL of MeOH:THF (1:1) was stirred at room temperature under N_2 for 16 h. The solution was concentrated then partitioned between CHCl_3 and 10% aq. NH_4OH . The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **450** (0.191 g, 89%) as a light yellow oil. MS (APCI) m/z 289 (100%) $[\text{M}+\text{H}]^+$.

Compound 451: To a stirring solution of **450** (0.191 g, 661 μmol) and ethyl formate (0.53 mL, 6.56 mmol) in benzene (10 mL) was added dropwise (via syringe) NaOMe (30 wt% in MeOH, 0.62 mL, 3.30 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **451** (0.211 g, >100%) as a yellow oil. MS (APCI) m/z 317 (100%) $[\text{M}+\text{H}]^+$.

Compound 452: A solution of slightly impure **451** (0.211 g, assume 0.661 mmol) in ethanol (10 mL) was treated with solid hydroxylamine hydrochloride (0.069 g, 0.99 mmol). The sample was heated at 50 $^\circ\text{C}$ under N_2 for 16 h, cooled to room temperature, concentrated, and partitioned between EtOAc and sat. NaHCO_3 . The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **452** (0.176 g, 85%) as a yellow oil. MS (APCI) m/z 314 (100%) $[\text{M}+\text{H}]^+$.

Compound 453: A solution of **452** (0.176 g, 0.561 mmol) in MeOH (10 mL) was treated with NaOMe (30 wt% in MeOH, 0.53 mL, 2.82 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated, and then partitioned between EtOAc and sat. KH_2PO_4 . The organic extract was washed with sat. NaCl solutions, dried (MgSO_4), filtered and concentrated to give **453** (0.170 g, 96%) as a yellow gummy solid. MS (APCI) m/z 314 (100%) $[\text{M}+\text{H}]^+$.

Compound TX63595: Dibromodimethylhydantoin (0.093 g, 0.325 mmol) was added to stirring solution of **453** (0.170 g, 0.541 mmol) in DMF (10 mL) at 0 °C under N₂. After stirring at 0 °C for 1 h, pyridine (0.44 mL, 5.44 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 16 h. The sample
5 was concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. NaHCO₃. The organic extract was washed with sat. KH₂PO₄ and sat. NaCl solution, dried (MgSO₄), filtered, and concentrated. Purification by chromatography (silica gel, 30% EtOAc/Hexanes) afforded **TX63595** (0.066 g, 39%) as an off-white foamy solid. ¹H NMR (500 MHz, d₆-DMSO) δ 8.86 (s, 1H), 3.96 (s,
10 3H), 2.80 (dd, 1H, J=17.5, 7.5 Hz), 2.56 (s, 3H), 2.48-2.54 (m, 1H), 2.12 (dd, 1H, J=12.5, 2.5 Hz), 1.98 (app dd, 1H, J=12.5, 7.5 Hz), 1.78-1.87 (m, 1H), 1.43 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 197.6, 169.1, 167.9, 165.8, 165.0, 114.8, 114.6, 111.5, 53.9, 46.1, 44.8, 42.8, 27.1, 25.6, 25.4, 21.4, 17.9. MS (ES) *m/z* 312 (M+23, 100%) and 312 (67%) [M+H]⁺.

Compound 454: To a stirring suspension at 0 °C under N₂ of **1** (4.67 g, 37.02 mmol) in 70 mL of acetonitrile was added dropwise 1-hexen-3-one (5 g, 46 mmol, 90+% stabilized with ~ 0.6% of 4-methoxyphenol) followed by dropwise addition of triethylamine (8.25 mL, 59.19 mmol). All solid was in solution towards the end of the triethylamine addition. The yellow solution was allowed to slowly warm to room
20 temperature overnight. The sample was concentrated, dissolved into EtOAc, washed with sat. NaHCO₃ and sat. NaCl solutions, dried (MgSO₄), filtered and concentrated to give 8.85 g (>100%) of crude **454** as a yellow liquid. MS (APCI) *m/z* 225 (17%) [M+H]⁺.

Compound 455: To a stirring solution at room temperature under N₂ of sl. crude **454** (entire amount from above, assume 37.02 mmol) in 150 mL of acetonitrile was added solid (R,S)-phenylalanine (6.11 g, 36.99 mmol) followed by addition of solid (1R)-(+)-10-camphorsulfonic acid (4.30 g, 18.51 mmol). The sample was heated under N₂ at 70 °C for 48 h, cooled to room temperature then filtered. The solid was washed with fresh acetonitrile, the combined filtrate was concentrated then
30 carefully partitioned between sat. NaHCO₃ solution and diethyl ether. The organic extract was washed with sat. NaCl solution dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 50% CHCl₃-10% EtOAc-40% hexanes). Separation was poor, all fractions containing a UV visible component (TLC, SiO₂ [10% EtOAc-40%

hexanes-50% CHCl₃], R_f ~ 0.45) were combined and concentrated to give 5.38 g (70%) of impure **455** as a light yellow liquid. (APCI) *m/z* 207 (100%) [M+H]⁺.

Compound 456: To a stirring solution at 0 °C under N₂ of impure **455** (6.101 g, 29.575 mmol) in 100 mL of EtOH was added dropwise a slightly cloudy solution of sodium borohydride (0.31 g, 8.19 mmol) in 50 mL of EtOH. After ~ 15 min (no starting material remains by TLC), the cold sample was quenched by dropwise addition of acetic acid (3.4 mL, 59.4 mmol), stirred at room temperature for 1 h then concentrated. The resultant light yellow gummy solid was dissolved into 200 mL of EtOAc containing 5 mL of water, dried with excess solid NaHCO₃ and filtered to give 5.92 g (96%) of impure **456** as a light yellow oil. MS (APCI) *m/z* 209 (100%) [M+H]⁺.

Compound 457: To a stirring solution at 0 °C under N₂ of sl. impure **456** (5.92 g, 28.42 mmol) and 3,4-dihydro-2H-pyran (3.6 mL, 39.6 mmol) in 100 mL of CH₂Cl₂ was added in one portion solid *p*-toluene- sulfonic acid monohydrate (0.50 g, 2.63 mmol). The sample immediately darkened (light yellow to brown) and was allowed to warm slowly to room temperature overnight. The dark sample was concentrated then partitioned between hexanes and sat. NaHCO₃ solution. The organic extract was washed with sat. KH₂PO₄ and sat. NaCl solutions, dried (MgSO₄), filtered , concentrated and chromatographed (silica gel, 20% EtOAc in hexanes) to give 3.868 g (46%) of **457** as light yellow oil. MS (APCI) *m/z* 293 (88%) [M+H]⁺ and 191 (100%).

Compound 458: Liquid ammonia (~5 mL) was condensed in a two-necked flask at -78 °C. Lithium wire (0.185 g, 26.66 mmol, 2 eq) was added in small portions. After 45 min, the lithium wire was dissolved then a solution of **457** (3.868 g, 13.227 mmol) in 15 mL of THF was added dropwise. The reaction mixture was stirred for 45 min at -78 °C then solid ammonium chloride (5 g, 93 mmol) was added and the ammonia was allowed to evaporate. The residue was dissolved into 100 mL of water and extracted with EtOAc (2x). The combined organic layer was concentrated and chromatographed (silica gel, 10% EtOAc in hexanes) to give 2.649 g (68%) of **458** as colorless oil. MS (APCI) *m/z* 175 (100%) [M+H]⁺.

Compound 459: A solution of **458** (2.649 g, 8.997 mmol) and pyridinium *p*-toluenesulfonate (0.23 g, 0.92 mmol) in 50 mL of EtOH was heated at 70 °C under N₂ for 6 h then room temperature overnight. The sample was concentrated then partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was

washed with sat. KH_2PO_4 and sat. NaCl solutions, dried (MgSO_4), filtered and concentrated to give 2.112 g (>100%) of sl. crude **459** as yellow oil. MS (APCI) m/z 211 (24%) $[\text{M}+\text{H}]^+$ and 175 (100%).

Compound 460: A solution under N_2 of sl. crude **459** (2.112 g, assume 8.997 mmol), ethylene glycol (5.0 mL, 89.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.171 g, 0.899 mmol) in 100 mL of benzene was refluxed under Dean-Stark conditions for 16 h. The sample was concentrated then partitioned between EtOAc and sat. NaHCO_3 solution. The organic extract was washed with sat. KH_2PO_4 and sat. NaCl solutions, dried (MgSO_4), filtered and concentrated to give 2.388 g (>100%) of crude **460** as dark yellow oil. MS (APCI) m/z 255 (35%) $[\text{M}+\text{H}]^+$ and 175 (100%).

Compound 461: To a stirring solution at room temperature of sl. crude **460** (2.388 g, assume 8.997 mmol) in 100 mL of CH_2Cl_2 was added solid MgSO_4 (1.08 g, 8.97 mmol) followed by solid pyridinium dichromate (6.77 g, 17.99 mmol). The sample was stirred at room temperature for 24 h, concentrated, suspended in 100 mL of diethyl ether, stirred at room temperature for 30 min and filtered. The filtrate was concentrate and chromatographed (silica gel, 30% EtOAc in hexanes) to give 1.513 g (67%) of **461** as white solid. MS (APCI) m/z 253 (79%) $[\text{M}+\text{H}]^+$ and 173 (100%).

Compound 462: To a stirring solution at 0 °C under N_2 of **461** (1.513 g, 5.995 mmol) and ethyl formate (5 mL, 62 mmol) in 10 mL of benzene was added sodium methoxide, 30 wt.% solution in methanol (6 mL, 32 mmol). The sample was allowed to slowly warm to room temperature overnight. The sample was dissolved in EtOAc, washed with sat. KH_2PO_4 and sat. NaCl solutions, dried (MgSO_4), filtered and concentrated to give 1.624 g (97%) of **462** as yellow gummy solid. MS (APCI) m/z 295 (100%) $[\text{M}+\text{H}]^+$.

Compound 463: A solution of **462** (1.206 g, 4.303 mmol) in EtOH (20 mL) was treated with methylhydrazine (0.46 mL, 8.65 mmol). The sample was sealed, heated at 50 °C for 16 h, cooled, concentrated, and then partitioned between CHCl_3 and 10% aq. NH_4OH . The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered, concentrated and chromatographed (silica gel, 50% EtOAc in hexanes) to afford **463** (0.989 g, 78%) as a gummy white solid. MS (APCI) m/z 291 (100) $[\text{M}+\text{H}]^+$.

Compound 464: A solution of **463** (0.320 g, 1.102 mmol) and 3 N HCl (4 mL, 12 mmol) MeOH/THF (1:1, 20 mL) was stirred at room temperature under N_2 for 16 h. The solution was concentrated and then partitioned between CHCl_3 and 10%

aq. NH_4OH . The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **464** (0.287 g, >100%) as a light yellow oil. MS (APCI) m/z 247 (100%) $[\text{M}+\text{H}]^+$.

Compound 465: To a stirring solution at room temperature under N_2 of slightly impure **464** (0.287 g, assume 1.102 mmol) and ethyl formate (0.89 mL, 11.02 mmol) in benzene (10 mL) was added dropwise (via syringe) NaOMe (30 wt% in MeOH, 1.0 mL, 5.5 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **465** (0.296 g, 98%) as a yellow oil. MS (APCI) m/z 276 (100%) and 275 (90%) $[\text{M}+\text{H}]^+$.

Compound 466: A solution of **465** (0.296 g, assume 1.077 mmol) in EtOH (10 mL) was treated with solid hydroxylamine hydrochloride (0.12 g, 1.73 mmol). The sample was heated at 50 °C under N_2 for 16 h, cooled, concentrated then partitioned between CHCl_3 and 10% aq. NH_4OH . The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **466** (0.273 g, 93%) as a dark yellow-brown oil. MS (APCI) m/z 273 (100%) and 272 (86%) $[\text{M}+\text{H}]^+$.

Compound 467: A solution of **466** (0.273 g, 1.006 mmol) in MeOH (10 mL) was treated with NaOMe (30 wt% in MeOH, 0.94 mL, 5.01 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **467** (0.226 g, 83%) as a dark yellow foamy solid. MS (APCI) m/z 273 ($\text{M}+2$, 100%) and 272 (85%) $[\text{M}+\text{H}]^+$.

Compound TX63589: To stirring solution at 0 °C under N_2 of **467** (0.226 g, 0.834 mmol) in DMF (10 mL) was added in one portion solid 1,3-dibromo-5,5-dimethyl-hydantoin (0.143 g, 0.500 mmol). After stirring at 0 °C for 1 h, pyridine (0.68 mL, 8.41 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 16 h. The sample was concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. NaHCO_3 solution. The organic extract was washed with sat. KH_2PO_4 and sat. NaCl solution, dried (MgSO_4), filtered, concentrated then chromatographed (silica gel, 50% EtOAc/Hexanes) to give **TX63589** (0.068 g, 30%) as an off-white foamy solid. ^1H NMR (500 MHz, CDCl_3) δ 8.36 (s, 1H), 7.06 (s, 1H), 3.83 (s, 3H), 2.74 (dd, 1H, $J = 15.0, 5.0$ Hz), 2.50–2.55 (m,

2H), 2.19–2.31 (m, 2H), 1.95 (app dd, 1H, $J = 15.0, 5.0$ Hz), 1.62–1.71 (m, 2H), 1.39 (s, 3H), 0.81 (t, 3H, $J = 7.5$ Hz); MS (APCI) m/z 270 (100%) $[M+H]^+$.

Compound 468: A mixture of **462** (0.412 g, 1.471 mmol), benzamidine hydrochloride (2.3 g, 16.68 mmol) and piperidine (0.87 mL, 8.80 mmol) in 2-propanol (10 mL) was heated in a sealed vial at 85 °C for 96 h. The sample was cooled, concentrated then partitioned between $CHCl_3$ and 10% aq. NH_4OH . The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **468** (0.910 g, >100%) as a brown-yellow solid, which was used without purification. MS (APCI) m/z 365 (100) $[M+H]^+$.

Compound 469: A solution of slightly impure **468** (0.910 g, assume 1.471 mmol) and 3 N HCl (10 mL, 30 mmol) in MeOH/THF (1:1, 20 mL) was stirred at room temperature under N_2 for 16 h. The solution was concentrated then partitioned between $CHCl_3$ and 10% aq. NH_4OH solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **469** (0.778 g, >100%) as a dark yellow gummy solid, which was used without purification. MS (APCI) m/z 321 (100%) $[M+H]^+$.

Compound 470: To a stirring solution at room temperature under N_2 of slightly crude **469** (0.778 g, assume 1.471 mmol) and ethyl formate (1.20 mL, 14.80 mmol) in benzene (10 mL) was added dropwise (via syringe) NaOMe (30 wt% in MeOH, 1.40 mL, 7.46 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **470** (0.684 g, >100%) as a dark yellow oil, which was used without purification. MS (APCI) m/z 349 (100%) $[M+H]^+$.

Compound 471: A solution of slightly impure **470** (0.684 g, assume 1.471 mmol) in EtOH (10 mL) was treated with solid hydroxylamine hydrochloride (0.15 g, 2.16 mmol). The sample was heated at 50 °C under N_2 for 16 h, cooled, concentrated then partitioned between EtOAc and sat. $NaHCO_3$ solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **471** (0.639 g, >100%) as a dark yellow oil, which was used without purification.

Compound 472: A solution of slightly impure **471** (0.639 g, assume 1.471 mmol) in MeOH (20 mL) was treated with NaOMe (30 wt% in MeOH solution (1.38 mL, 7.36 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic

extract was washed with sat. NaCl solutions, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to give **472** (0.267 g, 52%) as an off-white foamy solid. MS (APCI) *m/z* 368 (100%) [M+Na]⁺ and 346 (45%) [M+H]⁺.

5 **Compound TX63598**: To stirring solution at 0 °C under N₂ of **472** (0.267 g, 0.773 mmol) in DMF (10 mL) was added in one portion solid 1,3-dibromo-5,5-dimethyl-hydantoin (0.12 g, 0.42 mmol). After stirring at 0 °C for 1 h, pyridine (0.63 mL, 7.79 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 16 h. The sample was concentrated (to remove most of the DMF and
10 pyridine) then partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. KH₂PO₄ and sat. NaCl solutions, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/Hexanes) to afford **TX63598** (0.209 g, 79%) as an off-white foamy solid. ¹H NMR (500 MHz, CDCl₃) δ 8.96 (s, 1H), 8.59 (s, 1H), 8.44–8.46 (m, 2H), 7.48–7.53 (m, 3H), 3.01 (dd, 15 1H, *J* = 20.0, 5.0 Hz), 2.87–2.94 (m, 1H), 2.59 (app dt, 1H, *J* = 12.5, 5.0 Hz), 2.41 (td, 1H, *J* = 12.5, 3.3 Hz), 2.23–2.31 (m, 1H), 2.11–2.16 (m, 1H), 1.69–1.86 (m, 2H), 1.46 (s, 3H), 0.84 (t, 3H, *J* = 7.5 Hz); MS (ES) *m/z* 366 (100%) [M+H]⁺ and 344 (37%) [M+H]⁺.

Compound 473: To a stirring solution of **463** (0.661 g, 2.275 mmol) in
20 CH₂Cl₂ (10 L) was added in one portion solid 1,3-dibromo-5,5-dimethylhydantoin (0.36 g, 1.26 mmol). The solution immediately turned yellow-orange and all solid went into solution. The solution was stirred at room temperature for 30 min (TLC showed no starting material left), concentrated then partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. KH₂PO₄ and sat.
25 NaCl solutions, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 50% EtOAc/Hexanes) to give **473** (0.490 g, 58%) as colorless oil. MS (APCI) *m/z* 369/371 (100/64%) [M+H]⁺.

Compound 474: To a stirring degassed mixture of **473** (0.490 g, 1.327 mmol), potassium phosphate (0.85 g, 4.00 mmol) and phenylboronic acid (0.24 g, 1.97 mmol)
30 in DME (10 mL) was added in one portion solid tetrakis(triphenylphosphine) palladium (0) (0.153 g, 0.132 mmol). The sample was degassed, heated at 80 °C under N₂ for 16 h, cooled and filtered through a pad of Celite. The filtrate was concentrated, dissolved into EtOAc, washed with 1N NaOH, sat. KH₂PO₄ and sat. NaCl solutions, dried (MgSO₄), filtered, concentrated and chromatographed (silica

gel, 50% EtOAc/Hexanes) to give **474** (0.201 g, 41%) as an off-white solid. MS (APCI) m/z 367 (100%) $[M+H]^+$.

Compound 475: A solution of **474** (0.201 g, 0.548 mmol) and 3N HCl (4 mL, 12 mmol) in MeOH (20 mL) was stirred at room temperature under N₂ for 16 h. The sample was concentrated then carefully partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **475** (0.163 g, 92%) as an off-white foamy solid. MS (APCI) m/z 323 (100%) $[M+H]^+$.

Compound 476: To a stirring solution of **475** (0.163 g, 0.505 mmol) and ethyl formate (4.1 mL, 50.8 mmol) in benzene (10 mL) was added dropwise (via syringe) NaOMe (30 wt% solution in MeOH, 0.47 mL, 2.50 mmol). The sample was stirred at room temperature under N₂ for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **476** (0.187 g, >100%) as a yellow gummy solid, which was used without purification. MS (APCI) m/z 351 (100%) $[M+H]^+$.

Compound 477: A solution of slightly impure **476** (0.187 g, assume 0.505 mmol) and hydroxylamine hydrochloride (0.53 g, 0.76 mmol) in EtOH (20 mL) was heated at 50 °C under N₂ for 16 h. The sample was cooled, concentrated and partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **477** (0.181 g, >100%) as a dark yellow-brown oil, which was used without purification. MS (APCI) m/z 348 (100%) $[M+H]^+$.

Compound 478: To a stirring solution of slightly impure **477** (0.181 g, assume 0.505 mmol) at room temperature under N₂ in MeOH (20 mL) was added dropwise (via syringe) NaOMe (30 wt% solution in MeOH, 0.47 mL, 2.50 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **478** (0.204 g, >100%) as a dark yellow oil, which was used without purification. MS (APCI) m/z 348 (100%) $[M+H]^+$.

Compound TX63599: To a stirring solution at 0 °C under N₂ of slightly impure **478** (0.204 g, assume 0.505 mmol) in DMF (10 mL) was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.072 g, 0.252 mmol). After stirring at 0 °C for

1 h, pyridine (0.63 mL, 7.79 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 16 h. The sample was concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. KH₂PO₄ and sat. NaCl solutions, dried
5 (MgSO₄), filtered, concentrated and chromatographed (silica gel, 50% EtOAc/Hexanes) to give **TX63599** (0.052 g, 30% over 4 steps) as a yellow solid. ¹H NMR (500 MHz, CDCl₃) δ 8.48 (s, 1H), 7.45–7.48 (m, 2H), 7.39–7.42 (m, 1H), 7.31–7.33 (m, 2H), 3.79 (s, 3H), 2.53–2.65 (m, 3H), 2.35 (t, 1H, *J* = 12.5 Hz), 2.22–2.25 (m, 1H), 1.95–1.99 (m, 1H), 1.66–1.70 (m, 2H), 1.45 (s, 3H), 0.82 (t, 3H, *J* = 7.5 Hz);
10 MS (APCI) *m/z* 346 (100%) [M+H]⁺.

Compound 479: Hydrazine hydrochloride (86 mg, 1.26 mmol) was suspended in dioxane (2 mL) and triethylamine (0.18 mL, 1.26 mmol) was added followed by acetic acid (0.19 g, 3.15 mmol). The mixture was sonicated for several minutes. A solution of **276** (0.24 g, 0.63 mmol) in dioxane (4 mL) was added, and the mixture
15 was heated at 70 °C for 3 h. The mixture was cooled, diluted with sat. NaHCO₃ (20 mL), and 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 0.215 g (96%) of **479** as a white solid. APCI MS: *m/z* 358.1 [M+H]⁺.

Compound 480: Sodium hydride (72 mg, 1.80 mmol) was suspended in DMF
20 (2 mL). Compound **479** (215 mg, 0.60 mmol) was added, and the mixture was stirred for 30 min. Isopropyl iodide (0.30 mL, 3.01 mmol) was added and the mixture was stirred overnight. The reaction was quenched by the addition of sat. NH₄Cl (20 mL), and 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
25 a light yellow oil. Flash chromatography (EtOAc) gave 190 mg (79%) of **480** as a white foam. APCI MS: *m/z* 400.2 [M+H]⁺.

Compound 481: Compound **480** (185 mg, 0.46 mmol) was taken up in THF (4 mL) and 1M HCl (1 mL) was added. The solution was stirred 2 d, then diluted with sat. NaHCO₃ (20 mL) and extracted with EtOAc (2×50 mL). The combined
30 organic extracts were washed with brine (20 mL), dried over MgSO₄ and concentrated to give 160 mg (97%) of **481** as a white foam. APCI MS: *m/z* 356.0 [M+H]⁺.

Compound 482: Compound **481** (160 mg, 0.45 mmol) was taken up in THF (4 mL) and ethyl formate (1 mL) and cooled in an ice bath. NaOMe (0.8 g, 30 wt. % in MeOH) was added dropwise, and the solution was allowed to warm to RT and

stirred overnight. The mixture was quenched by the addition of sat. aq. KH_2PO_4 (20 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO_4 , and concentrated to give 170 mg (98%) of **482** as a white solid. APCI MS: m/z 384.1 $[\text{M}+\text{H}]^+$.

5 **Compound 483:** Compound **482** (170 mg, 0.44 mmol) was taken up in THF (4 mL), EtOH (2 mL), and water (0.5 mL). Hydroxylamine hydrochloride (46 mg, 0.66 mmol) was added and the reaction was heated at 50 °C for 3 h, then allowed to cool to room temperature and stirred overnight. After concentration, the residue was diluted with sat. aq. NaHCO_3 (20 mL) and extracted with EtOAc (2×50 mL). The
10 combined organic extracts were washed with brine (20 mL), dried over MgSO_4 , concentrated, and dried under vacuum to give 170 mg (100%) of **483** as an off-white solid. APCI MS: m/z 381.1 $[\text{M}+\text{H}]^+$.

Compound 484: Compound **483** (170 mg, 0.44 mmol) was taken up in THF (4 mL) and MeOH (2 mL) and NaOMe (0.8 g, 30 wt. % in MeOH) was added. The
15 solution was heated at 50 °C for 3 h, then cooled and concentrated. Sat. 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. Flash chromatography (70% EtOAc/DCM) gave 121 mg (72%) of **484** as a white foam. APCI MS: m/z 381.1 $[\text{M}+\text{H}]^+$.

20 **Compound TX63905:** Compound **484** (120 mg, 0.32 mmol) was taken up in DMF (3 mL) and cooled in an ice bath. *N,N'*-Dibromodimethylhydantoin (54 mg, 0.19 mmol) was added and the solution was stirred 90 min. at 0 °C. Pyridine (0.5 mL) was added and the solution was heated at 60 °C for 4 h. After cooling, the solution was concentrated and dried under vacuum to a light brown solid. Flash
25 chromatography (3:1 EtOAc/DCM) gave 82 mg (69%) of **TX63905** as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 8.50 (s, 1H), 8.10 (s, 1H), 4.52–4.63 (m, 1H), 4.17 (s, 3H), 3.08 (dd, 1H, $J = 5.2, 17.2$ Hz), 2.66–2.77 (m, 1H), 2.20 (dd, 1H, $J = 2.0, 11.6$ Hz), 1.80–1.99 (m, 2H), 1.58 (d, 6H, $J = 6.8$ Hz), 1.49 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H); APCI MS m/z 379.1 $[\text{M}+\text{H}]^+$.

30 **Compound TX63834:** A solution of **TX63465** (33 mg, 0.1 mmol) in MeCN (5 mL) was treated with 30% H_2O_2 (0.27 mL), and stirred at RT overnight. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2×15 mL). The organic layer was dried with MgSO_4 , and purified by column

chromatography (silica gel, 5–25% EtOAc/Hexanes) to give **TX63834** as white solid (30 mg, 85%). ^1H NMR (400 MHz, CDCl_3) δ 7.37–7.49 (m, 3H), 7.28–7.34 (m, 2H), 4.77 (s, 1H), 3.79 (s, 3H), 2.58 (dd, 1H, $J = 5.6, 15.6$ Hz), 2.36–2.54 (m, 2H), 1.72–1.80 (m, 1H), 1.58–1.70 (m, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H); MS: m/z [M+H] $^+$ 362.

Compound TX63848: A solution of **TX64541** (80 mg, 0.24 mmol) in MeCN (7 mL) was treated with 30% H_2O_2 (0.63 mL), stirred at RT overnight. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2×15 mL). The organic layer was dried with MgSO_4 , and purified by column chromatography (silica gel, 5–35% EtOAc/Hexanes) to give **TX63848** as a light yellow solid (8 mg, 10%). ^1H NMR (400 MHz, CDCl_3) δ 7.26–7.54 (m, 5H), 4.77 (s, 1H), 3.79 (s, 3H), 2.45–2.64 (m, 3H), 2.10–2.24 (m, 3H), 1.25–1.35 (m, 3H), 1.30 (s, 3H); MS: m/z [M+H] $^+$ 348.

Compounds 485 and 486: To a stirring solution at 0 °C of **152** (0.37 g, 1.59 mmol) in 20 mL of CH_2Cl_2 was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.23 g, 0.80 mmol). The sample was stirred for 30 min. and while still cold, quenched with sat. NaHCO_3 solution (~100 mL). The sample was warmed to room temperature, concentrated then extracted with EtOAc. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated. The sample was chromatographed (silica gel, 80% EtOAc/Hexanes) to give **485** (0.27 g, 55%) as a white solid (MS [APCI] m/z 311/313 (M+1, 91/100%) and **486** (0.080 g, 14%) as a white solid. MS (APCI) m/z 359 (100%) [M+H] $^+$..

Compound 487: To a stirring solution of **486** (0.080 g, 0.22 mmol) and ethyl formate (1.8 mL, 22.3 mmol) in 10 mL of benzene was added dropwise (via syringe) NaOMe (30 wt.% solution in methanol, 0.42 mL, 2.24 mmol). The sample was stirred at room temperature under N_2 for 16 h, concentrated then partitioned between CHCl_3 and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **487** (0.067 g, 78%) as tan solid, which was used without purification. MS (APCI) m/z 387 (100%) [M+H] $^+$..

Compound 488: A solution of slightly impure **487** (0.067 g, 0.17 mmol) and hydroxylamine hydrochloride (0.018 g, 0.26 mmol) in 10 mL of ethanol was heated at 50 °C under N_2 for 2 h then room temperature overnight. The sample was concentrated and partitioned between CHCl_3 and sat. NaHCO_3 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **488** (0.067 g, ~100%) as tan solid, which was used without purification.

Compound 489: To a stirring solution of slightly impure **488** (0.067 g, assume 0.17 mmol) at room temperature under N₂ in 10 mL of methanol:THF (1:1) was added dropwise (via syringe) NaOMe (30 wt.% solution in methanol, 0.32 mL, 1.71 mmol). The sample was stirred at room temperature for 16 h, concentrated then
5 partitioned between CHCl₃ and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **489** (0.054 g, 81%) as yellow oil, which was used without purification.

Compound TX63776: To a stirring solution at 0 °C under N₂ of slightly impure **489** (0.054 g, 0.14 mmol) in 5 mL of DMF was added in one portion 1,3-
10 dibromo-5,5-dimethylhydantoin (0.020 g, 0.070 mmol). After stirring at 0 °C for 1 h, pyridine (0.12 mL, 1.48 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between CHCl₃ and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered,
15 concentrated and chromatographed (silica gel, 100% EtOAc) to give **TX63776** (0.014 g, 27%) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), [5.70 (s), 5.65 (s), 1H], [3.63 (s), 3.63 (s), 3H], 2.41 (m, 3H), 2.05 (*app.dt*, 2.2, 12.8, 1H), 1.93 (m, 1H), 1.65 (m, 1H), [1.53 (s), 1.52 (s), 3H], [1.50 (s), 1.49 (s), 3H], 1.37 (s, 3H), 1.21 (d, 3H, *J* = 6.8 Hz); MS (APCI) *m/z* 382 (100%) [M+H]⁺.

Compound 490: A solution of **386** (0.42 g, 1.16 mmol) in 10 mL of ethanol
20 was treated with sodium ethoxide, 21 wt. % solution in ethanol (2.2 mL, 5.9 mmol). The sample was flushed with N₂, sealed and heated at 80 °C for 48 h. The sample was cooled, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and
25 concentrated to give **490** (0.40 g, ~92%) as dark yellow oil, which was used without purification.

Compound 491: A solution of **490** (0.40 g, 1.07 mmol) and 3 N HCl (10 mL, 30 mmol) in 10 mL of ethanol was stirred at room temperature under N₂ for 16 h. The sample was concentrated, cooled, basified with 10% aq. NH₄OH solution to a pH
30 ~ 9–10 and extracted with EtOAc. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **491** (0.35 g, 99%) as a yellow solid, which was used without purification. MS (APCI) *m/z* 331 (100%) [M+H]⁺.

Compound 492: To a stirring solution of **491** (0.35 g, 1.06 mmol) and ethyl formate (10 mL, 124 mmol) in 10 mL of benzene was added dropwise (via syringe) sodium ethoxide, 21 wt.% solution in ethanol (2.0 mL, 5.4 mmol). The sample was stirred at room temperature under N₂ for 16 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **492** (0.38 g, ~100%) as a dark yellow oil, which was used without purification. MS (APCI) *m/z* 359 (100%) [M+H]⁺.

Compound 493: A solution of **492** (0.38 g, 1.06 mmol) and hydroxylamine hydrochloride (0.11 g, 1.58 mmol) in 10 mL of ethanol was heated at 50 °C under N₂ for 2 h then room temperature overnight. The sample was concentrated and partitioned between EtOAc and sat. NaHCO₃ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered and concentrated to give **493** (0.33 g, 88%) as dark yellow oil, which was used without purification. MS (APCI) *m/z* 378 (100%) and 356 (88%) [M+H]⁺.

Compound 494: To a stirring solution of slightly impure **493** (0.33 g, 0.93 mmol) at room temperature under N₂ in 20 mL of ethanol was added dropwise (via syringe) sodium ethoxide, 21 wt.% solution in ethanol (1.75 mL, 4.69 mmol). The sample was stirred at room temperature for 72 h, concentrated then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated to give **494** (0.32 g, 96 %) as a dark yellow foamy solid. MS (APCI) *m/z* 356 (100%) [M+H]⁺.

Compound TX63900: To a stirring solution at 0 °C under N₂ of **494** (0.32 g, 0.89 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.125 g, 0.44 mmol). After stirring at 0 °C for 1 h, pyridine (0.72 mL, 8.90 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. KH₂PO₄ solution. The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated, chromatographed (silica gel, 20% EtOAc/hexanes) then crystallized from cold hexanes to give **TX63900** (0.097 g, 31%) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.85 (s, 1H), 4.42 (q, 2H, *J* = 6.8 Hz), 2.53 (dd, 1H, *J* = 6.4, 18.4 Hz), 2.45–2.55 (m, 2H), 1.98–2.10 (m, 2H), 1.60–1.73 (m, 1H), 1.35 (s, 3H), 1.35 (t, 3H, *J*

= 7.2 Hz), 1.33 (s, 9H), 1.26 (d, 3H, $J = 6.8$ Hz); MS (APCI) m/z 354 (100%) $[M+H]^+$.

Compound 495: To a stirring solution at room temperature under N_2 of **127** (1.00 g, 4.20 mmol) and dimethyl carbonate (7.1 mL, 84.2 mmol) in 10 mL of THF was added portionwise sodium hydride, 60% dispersion in mineral oil (0.67 g, 16.75 mmol). The solution was stirred at room temperature for 1 h, and then 80 °C overnight. The sample was cooled to room temperature, concentrated then partitioned between Et_2O and sat. aq. KH_2PO_4 . The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give the intermediate keto-ester (1.69 g, >100% as dark yellow oil. In a sealable vial, a solution of the intermediate (assume 4.20 mmol) in 10 mL of 2-propanol was treated with solid formamidine acetate (4.40 g, 42.26 mmol) followed by piperidine (2.1 mL, 21.2 mmol). The sample was flushed with N_2 , sealed and heated (via a block heater) at 80 °C for 72 h. The sample was cooled, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered, concentrated then chromatographed (silica gel, 30–50% EtOAc/hexanes) to give **495** (0.189 g, 16 %) as a light yellow solid. MS (APCI) m/z 291 (100%) $[M+H]^+$.

Compound 496: A solution of **495** (0.189 g, 0.652 mmol) and *N,N*-diisopropylethylamine (0.125 mL, 0.718 mmol) in 10 mL of benzene was added dropwise (via syringe) phosphorus oxychloride (0.61 mL, 6.54 mmol). After addition, the sample was heated at 90 °C under N_2 for 2 h, cooled, concentrated then carefully partitioned between EtOAc and sat. $NaHCO_3$ solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **496** (0.172 g, 86%) as a tan solid. MS (APCI) m/z 309/311 (100/42%) $[M+H]^+$.

Compound 497: A solution of **496** (0.172 g, 0.558 mmol) in 10 mL of methanol was treated with sodium methoxide, 30 wt.% solution in methanol solution (0.52 mL, 2.77 mmol). The sample was flushed with N_2 , sealed and heated at 60 °C for 16 h. The sample was cooled, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried ($MgSO_4$), filtered and concentrated to give **497** (0.151 g, 88%) as a yellow solid, which was used without purification. MS (APCI) m/z 305 (100%) $[M+H]^+$.

Compound 498: A solution of **497** (0.151 g, 0.496 mmol) and 3 N HCl (4 mL, 12 mmol) in 20 mL of methanol was stirred at room temperature under N_2 for 16

h. The sample was concentrated, cooled, basified with 10% aq. NH_4OH solution to a pH ~ 9 –10 and extracted with EtOAc. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **498** (0.128 g, 99%) as a dark yellow oil, which was used without purification. MS (APCI) m/z 261 (100%) $[\text{M}+\text{H}]^+$.

Compound 499: To a stirring solution of slightly impure **498** (0.128 g, 0.492 mmol) and ethyl formate (4.0 mL, 50 mmol) in 10 mL of benzene was added dropwise (via syringe) sodium methoxide, 30 wt.% solution in methanol (0.46 mL, 52.45 mmol). The sample was stirred at room temperature under N_2 for 48 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **499** (0.115 g, 82%) as light yellow solid, which was used without purification. MS (APCI) m/z 289 (100%) $[\text{M}+\text{H}]^+$.

Compound 500: A solution of slightly impure **499** (0.115 g, assume 0.401 mmol) and hydroxylamine hydrochloride (0.042 g, 0.604 mmol) in 10 mL of ethanol was heated at 50 °C under N_2 for 16 h, cooled, concentrated and partitioned between CHCl_3 and sat. NaHCO_3 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **500** (0.109 g, 95%) as a yellow oil, which was used without purification. MS (APCI) m/z 286 (100%) $[\text{M}+\text{H}]^+$.

Compound 501: To a stirring solution of slightly impure **500** (0.109 g, 0.381 mmol) at room temperature under N_2 in 10 mL of methanol was added dropwise (via syringe) sodium methoxide, 30 wt.% solution in methanol (0.36 mL, 1.92 mmol). The sample was stirred at room temperature for 16 h, concentrated then partitioned between EtOAc and sat. KH_2PO_4 solution. The organic extract was washed with sat. NaCl solution, dried (MgSO_4), filtered and concentrated to give **501** (0.096 g, 88%) as a yellow oil, which was used without purification. MS (APCI) m/z 286 (100%) $[\text{M}+\text{H}]^+$.

Compound TX63874: To a stirring solution at 0 °C under N_2 of slightly impure **501** (0.096 g, 0.338 mmol) in 10 mL of DMF was added in one portion 1,3-dibromo-5,5-dimethylhydantoin (0.048 g, 0.168 mmol). After stirring at 0 °C for 1 h, pyridine (0.27 mL, 3.34 mmol) was added. The ice bath was removed and the sample was heated at 50 °C for 2 h. The sample was cooled, concentrated (to remove most of the DMF and pyridine) then partitioned between EtOAc and sat. KH_2PO_4 solution.

The organic extract was washed with sat. NaCl solution, dried (MgSO₄), filtered, concentrated and chromatographed (silica gel, 30% EtOAc/hexanes) to give **TX63874** (0.028 g, 30%) as a tan solid. ¹H NMR (400 MHz, CDCl₃) δ 8.81 (s, 1H), 8.61 (s, 1H), 3.99 (s, 3H), 2.81 (dd, 1H, *J* = 6.4, 18.4 Hz), 2.49–2.64 (m, 2H), 2.00–2.15 (m, 2H), 1.64–1.77 (m, 1H), 1.39 (s, 3H), 1.29 (d, 3H, *J* = 8.8 Hz); MS (APCI) *m/z* 284 (100%) [M+H]⁺.

* * * * *

All of the methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes 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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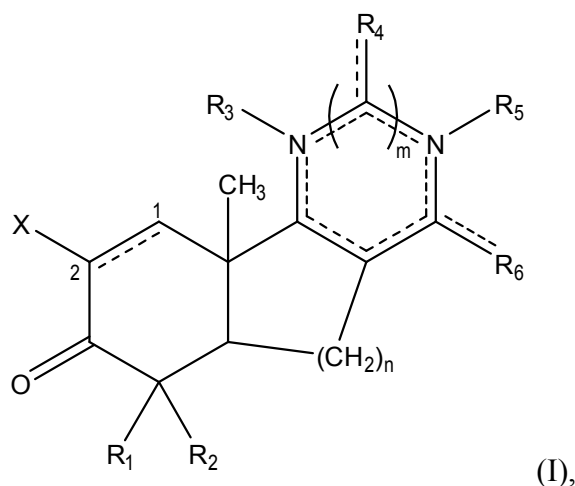
The following references to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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CLAIMS

1. A compound of the formula:



wherein:

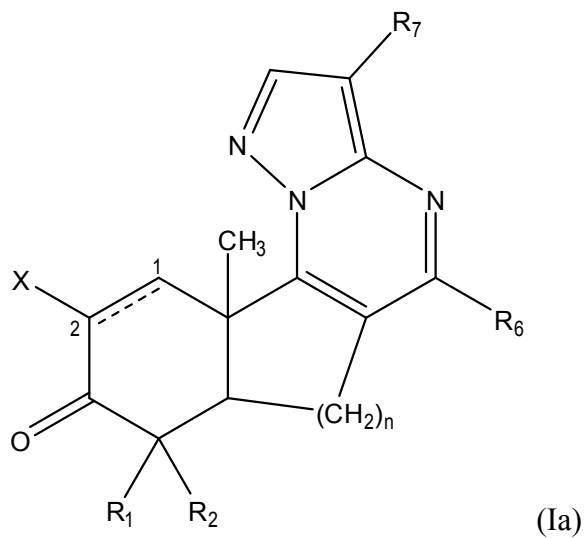
- the atoms labeled 1 and 2 are connected either by a double bond or an epoxidized double bond;
- n is 1 or 2;
- m is 0 or 1;
- X is $-\text{CN}$ or $-\text{CF}_3$;
- R_1 and R_2 are each independently hydrogen; or $\text{alkyl}_{(\text{C} \leq 12)}$, $\text{aryl}_{(\text{C} \leq 12)}$, $\text{aralkyl}_{(\text{C} \leq 12)}$, or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$; or
- R_1 and R_2 are taken together and are $\text{alkanediyl}_{(\text{C} \leq 12)}$;
- R_3 is absent, hydrogen; or $\text{alkyl}_{(\text{C} \leq 12)}$, $\text{aryl}_{(\text{C} \leq 12)}$, or a substituted version of either of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$; or R_3 is taken together with R_4 as provided below; provided that R_3 is absent when and only when the atom to which it is bound forms part of a double bond;

5 R_4 is hydrogen or oxo; or alkyl_(C≤12), aryl_(C≤12), heteroaryl_(C≤12), acyl_(C≤12),
 alkoxy_(C≤12), or a substituted version of any of these groups, wherein the
 term “substituted” means that one or more hydrogen atom has been
 independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂,
 –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃,
 –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂; or R_4 is taken
 together with either R_3 or R_5 as provided below;

10 R_5 is absent, hydrogen; or alkyl_(C≤12), aryl_(C≤12), acyl_(C≤12) or a substituted version
 of any of these groups, wherein the term “substituted” means that one or
 more hydrogen atom has been independently replaced by –OH, –F, –Cl,
 –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃,
 –OCH₂CH₃, –C(O)CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –
 S(O)₂NH₂; or R_5 is taken together with R_4 as provided below; provided
 15 that R_5 is absent when and only when the atom to which it is bound
 forms part of a double bond; and

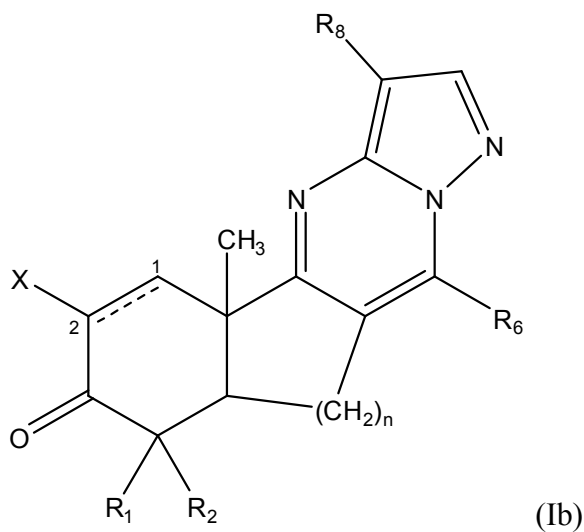
20 R_6 is hydrogen, hydroxy, amino, halo, cyano, or oxo; or alkyl_(C≤12), alkenyl_(C≤12),
 alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12),
 heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkylamino_(C≤12),
 dialkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these
 groups, wherein the term “substituted” means that one or more hydrogen
 atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂,
 –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃,
 –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂;

provided that when R_3 and R_4 are taken together, the compound is further defined by formula Ia:



wherein R_7 is hydrogen or halo; or aryl_(C≤12); or

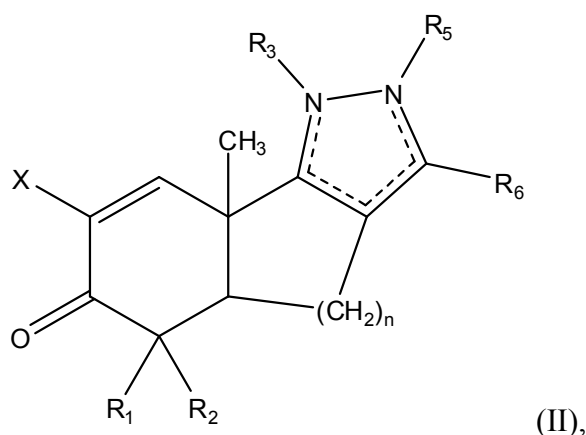
5 provided that when R_4 and R_5 are taken together, the compound is further defined by formula Ib:



wherein R_8 is hydrogen or halo;

or a pharmaceutically acceptable salt or tautomer thereof.

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



wherein:

n is 1 or 2;

X is $-\text{CN}$ or $-\text{CF}_3$;

R_1 and R_2 are each independently hydrogen; or $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$, $\text{aralkyl}_{(\text{C}\leq 12)}$, or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$; or

R_1 and R_2 are taken together and are $\text{alkanediyl}_{(\text{C}\leq 12)}$;

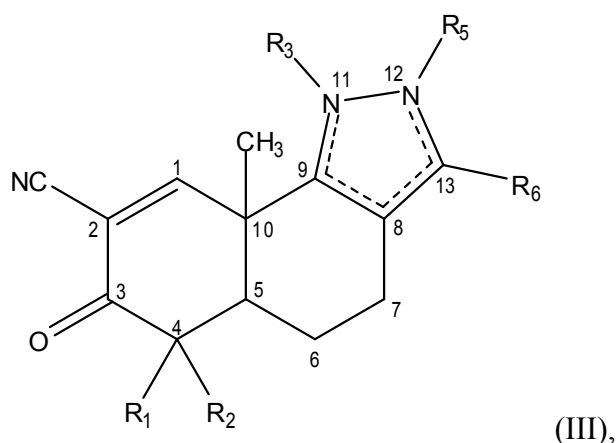
R_3 is absent, hydrogen; or $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$, or a substituted version of either of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$; provided that R_3 is absent when and only when the atom to which it is bound forms part of a double bond;

R_5 is absent, hydrogen; or $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$, $\text{acyl}_{(\text{C}\leq 12)}$ or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$; provided that R_5 is absent when and only when the atom to which it is bound forms part of a double bond; and

R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂;

or a pharmaceutically acceptable salt or tautomer thereof.

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



wherein:

R₁ and R₂ are each independently hydrogen; or alkyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂; or

R₁ and R₂ are taken together and are alkanediyl_(C≤12);

R₃ is absent, hydrogen; or alkyl_(C≤12), aryl_(C≤12), or a substituted version of either of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂; provided

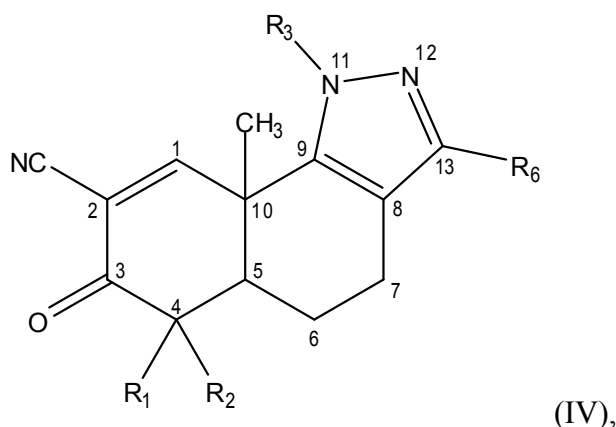
that R₃ is absent when and only when the atom to which it is bound forms part of a double bond;

R₅ is absent, hydrogen; or alkyl_(C≤12), aryl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂; provided that R₅ is absent when and only when the atom to which it is bound forms part of a double bond; and

R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂;

or a pharmaceutically acceptable salt or tautomer thereof.

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



wherein:

R₁ and R₂ are each independently hydrogen; or alkyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂,

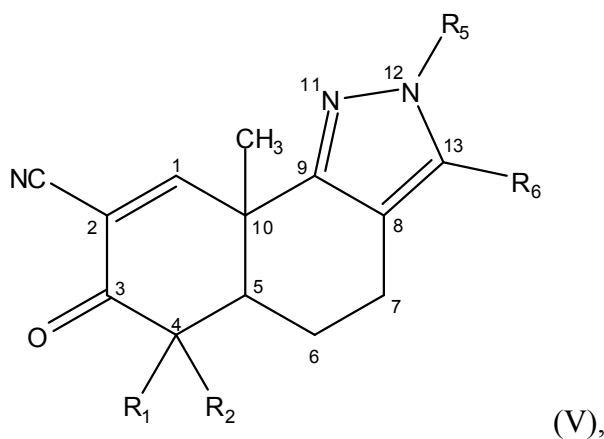
$-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$,
 $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$;

R_3 is hydrogen; or $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$, or a substituted version of either of
 these groups, wherein the term “substituted” means that one or more
 hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$,
 $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$; and

R_6 is hydrogen, hydroxy, amino, halo, or cyano; or $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{alkenyl}_{(\text{C}\leq 12)}$,
 $\text{alkynyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$, $\text{aralkyl}_{(\text{C}\leq 12)}$, $\text{heteroaryl}_{(\text{C}\leq 12)}$,
 $\text{heterocycloalkyl}_{(\text{C}\leq 12)}$, $\text{acyl}_{(\text{C}\leq 12)}$, $\text{alkoxy}_{(\text{C}\leq 12)}$, $\text{alkylamino}_{(\text{C}\leq 12)}$,
 $\text{dialkylamino}_{(\text{C}\leq 12)}$, $\text{amido}_{(\text{C}\leq 12)}$, or a substituted version of any of these
 groups, wherein the term “substituted” means that one or more hydrogen
 atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$,
 $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$,
 $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$;

or a pharmaceutically acceptable salt or tautomer thereof.

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



wherein:

R_1 and R_2 are each independently hydrogen; or $\text{alkyl}_{(\text{C}\leq 12)}$, $\text{aryl}_{(\text{C}\leq 12)}$,
 $\text{aralkyl}_{(\text{C}\leq 12)}$, or a substituted version of any of these groups, wherein the
 term “substituted” means that one or more hydrogen atom has been
 independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$,
 $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$,
 $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$; or

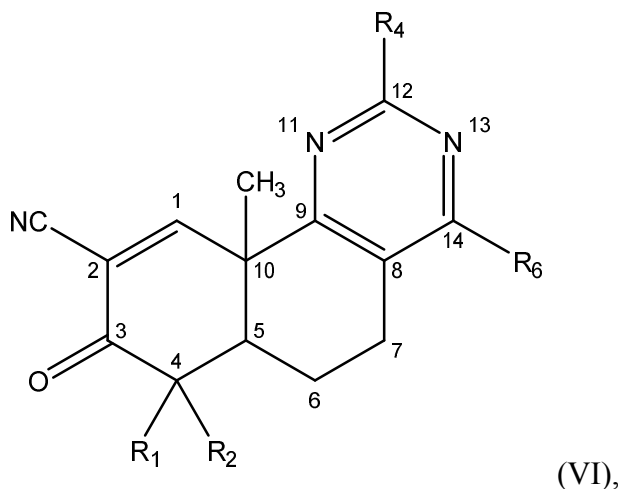
R₁ and R₂ are taken together and are alkanediyl_(C≤12);

R₅ is hydrogen; or alkyl_(C≤12), aryl_(C≤12), acyl_(C≤12) or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂; and

R₆ is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12), alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkylamino_(C≤12), dialkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂;

or a pharmaceutically acceptable salt or tautomer thereof.

6. The compound of claim 1, further defined as:



wherein:

R₁ and R₂ are each independently hydrogen; or alkyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂;

- 5 R_4 is hydrogen; or alkyl_(C≤12), aryl_(C≤12), heteroaryl_(C≤12), acyl_(C≤12), alkoxy_(C≤12),
 or a substituted version of any of these groups, wherein the term
 “substituted” means that one or more hydrogen atom has been
 independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂,
 –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃,
 –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂; and
 10 R_6 is hydrogen, hydroxy, amino, halo, or cyano; or alkyl_(C≤12), alkenyl_(C≤12),
 alkynyl_(C≤12), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12),
 heterocycloalkyl_(C≤12), acyl_(C≤12), alkoxy_(C≤12), alkylamino_(C≤12),
 dialkylamino_(C≤12), amido_(C≤12), or a substituted version of any of these
 groups, wherein the term “substituted” means that one or more hydrogen
 atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂,
 –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃,
 –N(CH₃)₂, –C(O)NH₂, –OC(O)CH₃, or –S(O)₂NH₂;
 15 or a pharmaceutically acceptable salt or tautomer thereof.
7. The compound of claim 1, wherein the atoms labeled 1 and 2 are connected by a double bond.
 8. The compound of claim 1, wherein the atoms labeled 1 and 2 are connected by an epoxidized double bond.
 - 20 9. The compound according to one of claims 1, 2, 7 and 8, wherein n is 1.
 10. The compound according to one of claims 1, 2, 7 and 8, wherein n is 2.
 11. The compound according to one of claims 1 and 7-10, wherein m is 0.
 12. The compound according to one of claims 1, and 7-10, wherein m is 1.
 13. The compound according to one of claims 1, 2 and 7-12, wherein X is –CN.
 - 25 14. The compound according to one of claims 1, 2 and 7-12, wherein X is –CF₃.
 15. The compound according to one of claims 1-14, wherein R_1 or R_2 is alkyl_(C≤8) or substituted alkyl_(C≤8), wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂,

$-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.

16. The compound according to one of claims 1-14, wherein R_1 or R_2 is $\text{alkyl}_{(\text{C}\leq 8)}$.
17. The compound of claim 16, wherein R_1 or R_2 is methyl.
- 5 18. The compound of claim 17, wherein R_1 and R_2 are each methyl.
19. The compound of claim 17, wherein R_1 is methyl and R_2 is hydrogen.
20. The compound of claim 16, wherein R_1 or R_2 is ethyl.
21. The compound of claim 20, wherein R_1 is ethyl and R_2 is hydrogen.
22. The compound according to one of claims 1-14, wherein R_1 or R_2 is hydrogen.
- 10 23. The compound of claim 22, wherein R_1 and R_2 are each hydrogen.
24. The compound according to one of claims 1-3, 5, 7-14, wherein R_1 and R_2 are taken together and are $\text{alkanediyl}_{(\text{C}\leq 8)}$.
25. The compound of claim 24, wherein R_1 and R_2 are taken together and are 1,4-butanediyl.
- 15 26. The compound according to one of claims 1-14, wherein R_1 or R_2 is $\text{aryl}_{(\text{C}\leq 8)}$.
27. The compound of claim 26, wherein R_1 or R_2 is phenyl.
28. The compound of claim 27, wherein R_1 is phenyl and R_2 is hydrogen.
29. The compound according to one of claims 1-14, wherein R_1 or R_2 is $\text{aralkyl}_{(\text{C}\leq 8)}$.
30. The compound of claim 29, wherein R_1 or R_2 is benzyl.
- 20 31. The compound of claim 30, wherein R_1 is benzyl and R_2 is hydrogen.
32. The compound of claim 30, wherein R_1 and R_2 are each benzyl.
33. The compound according to one of claims 1-3 and 7-32, wherein R_3 is absent.
34. The compound according to one of claims 1-4 and 7-32, wherein R_3 is hydrogen.

35. The compound according to one of claims 1-4 and 7-32, wherein R_3 is $\text{alkyl}_{(C\leq 8)}$, $\text{aryl}_{(C\leq 8)}$, or a substituted version of either of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$,
5 $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.
36. The compound of claim 35, wherein R_3 is $\text{alkyl}_{(C\leq 4)}$ or substituted $\text{alkyl}_{(C\leq 4)}$, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$,
 $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.
- 10 37. The compound of claim 36, wherein R_3 is $\text{alkyl}_{(C\leq 4)}$.
38. The compound of claim 36, wherein R_3 is methyl.
39. The compound of claim 35, wherein R_3 is $\text{aryl}_{(C\leq 8)}$ or substituted $\text{aryl}_{(C\leq 8)}$, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$,
15 $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.
40. The compound of claim 39, wherein R_3 is $\text{aryl}_{(C\leq 8)}$.
41. The compound of claim 40, wherein R_3 is phenyl.
42. The compound according to one of claims 1 and 6-41, wherein R_4 is hydrogen.
43. The compound according to one of claims 1 and 7-41, wherein R_4 is oxo.
- 20 44. The compound according to one of claims 1 and 6-41, wherein R_4 is $\text{alkyl}_{(C\leq 8)}$, $\text{aryl}_{(C\leq 8)}$, $\text{acyl}_{(C\leq 8)}$, $\text{alkoxy}_{(C\leq 8)}$ or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$,
 $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.
- 25 45. The compound of claim 44, wherein R_4 is $\text{alkyl}_{(C\leq 6)}$ or substituted $\text{alkyl}_{(C\leq 6)}$, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$,
 $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.

46. The compound of claim 45, wherein R₄ is alkyl_(C≤6).
47. The compound of claim 46, wherein R₄ is methyl, isopropyl, *t*-butyl, or cyclopropyl.
48. The compound of claim 45, wherein R₄ is haloalkyl_(C≤6).
49. The compound of claim 48, wherein R₄ is trifluoromethyl.
- 5 50. The compound of claim 44, wherein R₄ is alkoxy_(C≤6).
51. The compound of claim 50, wherein R₄ is methoxy or ethoxy.
52. The compound of claim 44, wherein R₄ is aryl_(C≤8) or substituted aryl_(C≤8), wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH,
10 -OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.
53. The compound of claim 52, wherein R₄ is phenyl, chlorophenyl, methylphenyl, or methoxyphenyl.
54. The compound according to one of claims 1 and 6-41, wherein R₄ is heteroaryl_(C≤8).
55. The compound of claim 54, wherein R₄ is pyridinyl or pyrimidinyl.
- 15 56. The compound of claim 44, wherein R₄ is acyl_(C≤6) or substituted acyl_(C≤6), wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH,
-OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.
57. The compound of claim 56, wherein R₄ is ethoxycarbonyl.
- 20 58. The compound according to one of claims 1-3 and 7-57, wherein R₅ is absent.
59. The compound according to one of claims 1-3 and 7-57, wherein R₅ is hydrogen.
60. The compound according to one of claims 1-3 and 7-57, wherein R₅ is alkyl_(C≤8), aryl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups, wherein the term “substituted” means that one or more hydrogen atom has been independently replaced

by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃,
-OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.

61. The compound of claim 60, wherein R₅ is alkyl_(C≤6) or substituted alkyl_(C≤6), wherein
the term “substituted” means that one or more hydrogen atom has been independently
5 replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH,
-OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.
62. The compound of claim 61, wherein R₅ is alkyl_(C≤6).
63. The compound of claim 61, wherein R₅ is methyl, cyclohexyl, or *t*-butyl.
64. The compound of claim 61, wherein R₅ is substituted alkyl_(C≤4), wherein the term
10 “substituted” means that one or more hydrogen atom has been independently replaced
by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃,
-OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.
65. The compound of claim 64, wherein R₅ is 2-hydroxyethyl or 2,2,2-trifluoroethyl.
66. The compound of claim 60, wherein R₅ is aryl_(C≤8) or substituted aryl_(C≤8), wherein the
15 term “substituted” means that one or more hydrogen atom has been independently
replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH,
-OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.
67. The compound of claim 66, wherein R₅ is aryl_(C≤8).
68. The compound of claim 67, wherein R₅ is phenyl.
- 20 69. The compound of claim 60, wherein R₅ is acyl_(C≤8) or substituted acyl_(C≤8), wherein the
term “substituted” means that one or more hydrogen atom has been independently
replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH,
-OCH₃, -OCH₂CH₃, -C(O)CH₃, -N(CH₃)₂, -C(O)NH₂, -OC(O)CH₃, or -S(O)₂NH₂.
70. The compound of claim 69, wherein R₅ is acetyl, methoxycarbonyl, ethoxycarbonyl, or
25 phenylcarbonyl.
71. The compound according to one of claims 1-70, wherein R₆ is hydrogen.
72. The compound according to one of claims 1-70, wherein R₆ is cyano.

73. The compound according to one of claims 1-70, wherein R_6 is halo.
74. The compound of claim 73, wherein R_6 is chloro or bromo.
75. The compound according to one of claims 1-70, wherein R_6 is $\text{alkyl}_{(C \leq 6)}$ or substituted $\text{alkyl}_{(C \leq 6)}$, wherein the term "substituted" means that one or more hydrogen atom has
5 been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.
76. The compound of claim 75, wherein R_6 is $\text{alkyl}_{(C \leq 6)}$.
77. The compound of claim 76, wherein R_6 is methyl, isopropyl or cyclohexyl.
- 10 77. The compound of claim 76, wherein R_6 is methyl, isopropyl or cyclohexyl.
78. The compound according to one of claims 1-70, wherein R_6 is $\text{aryl}_{(C \leq 8)}$, $\text{heteroaryl}_{(C \leq 8)}$ or a substituted version of either of these groups, wherein the term "substituted" means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$,
15 $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.
79. The compound according to one of claims 1-70, wherein R_6 is $\text{aryl}_{(C \leq 10)}$.
80. The compound of claim 79, wherein R_6 is phenyl, methylphenyl or naphthyl.
81. The compound of claim 78, wherein R_6 is substituted $\text{aryl}_{(C \leq 8)}$, wherein the term
20 "substituted" means that one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OC}(\text{O})\text{CH}_3$, or $-\text{S}(\text{O})_2\text{NH}_2$.
82. The compound of claim 81, wherein R_6 is chlorophenyl, fluorophenyl or methoxyphenyl.
83. The compound of claim 78, wherein R_6 is $\text{heteroaryl}_{(C \leq 8)}$.
- 25 84. The compound of claim 83, wherein R_6 is pyridinyl, pyrimidinyl, methylpyrazolyl, dimethylisoxazolyl, methyltriazolyl, or methyltetrazolyl.

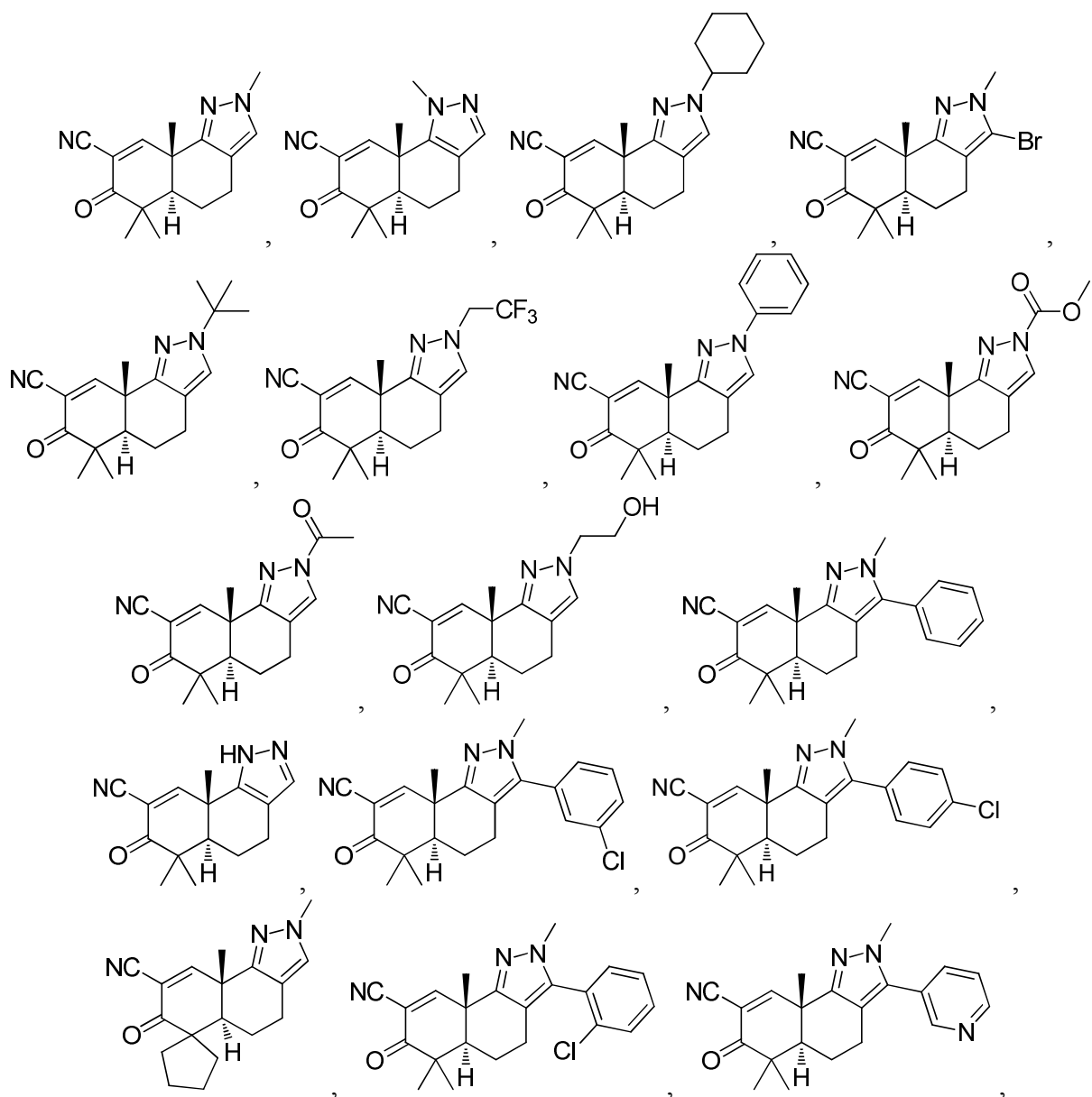
85. The compound according to one of claims 1-70, wherein R_6 is aralkyl_(C≤12) or substituted aralkyl_(C≤12), wherein the term “substituted” means that one or more hydrogen atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$.
86. The compound of claim 85, wherein R_6 is benzyl.
87. The compound according to one of claims 1-70, wherein R_6 is amido_(C≤8).
88. The compound of claim 87, wherein R_6 is phenylcarbonylamino.
89. The compound according to one of claims 1-70, wherein R_6 is alkynyl_(C≤8).
90. The compound of claim 89, wherein R_6 is ethynyl.
91. The compound according to one of claims 1-70, wherein R_6 is acyl_(C≤8).
92. The compound according to one of claims 1-70, wherein R_6 is aminocarbonyl or dimethylaminocarbonyl.
93. The compound according to one of claims 1-70, wherein R_6 is alkoxy_(C≤8).
94. The compound of claim 93, wherein R_6 is methoxy.
95. The compound according to one of claims 1, 7-32 and 71-94, wherein R_7 or R_8 is hydrogen.
96. The compound according to one of claims 1, 7-32 and 71-94, wherein R_7 or R_8 is halo.
97. The compound of claim 96, wherein R_7 or R_8 is bromo.
98. The compound according to one of claims 1, 7-32 and 71-94, wherein R_7 is aryl_(C≤8).
99. The compound of claim 98, wherein R_7 is phenyl.
100. The compounds according to any one of claims 3-94, wherein carbon atom 10 is in the *R* configuration.

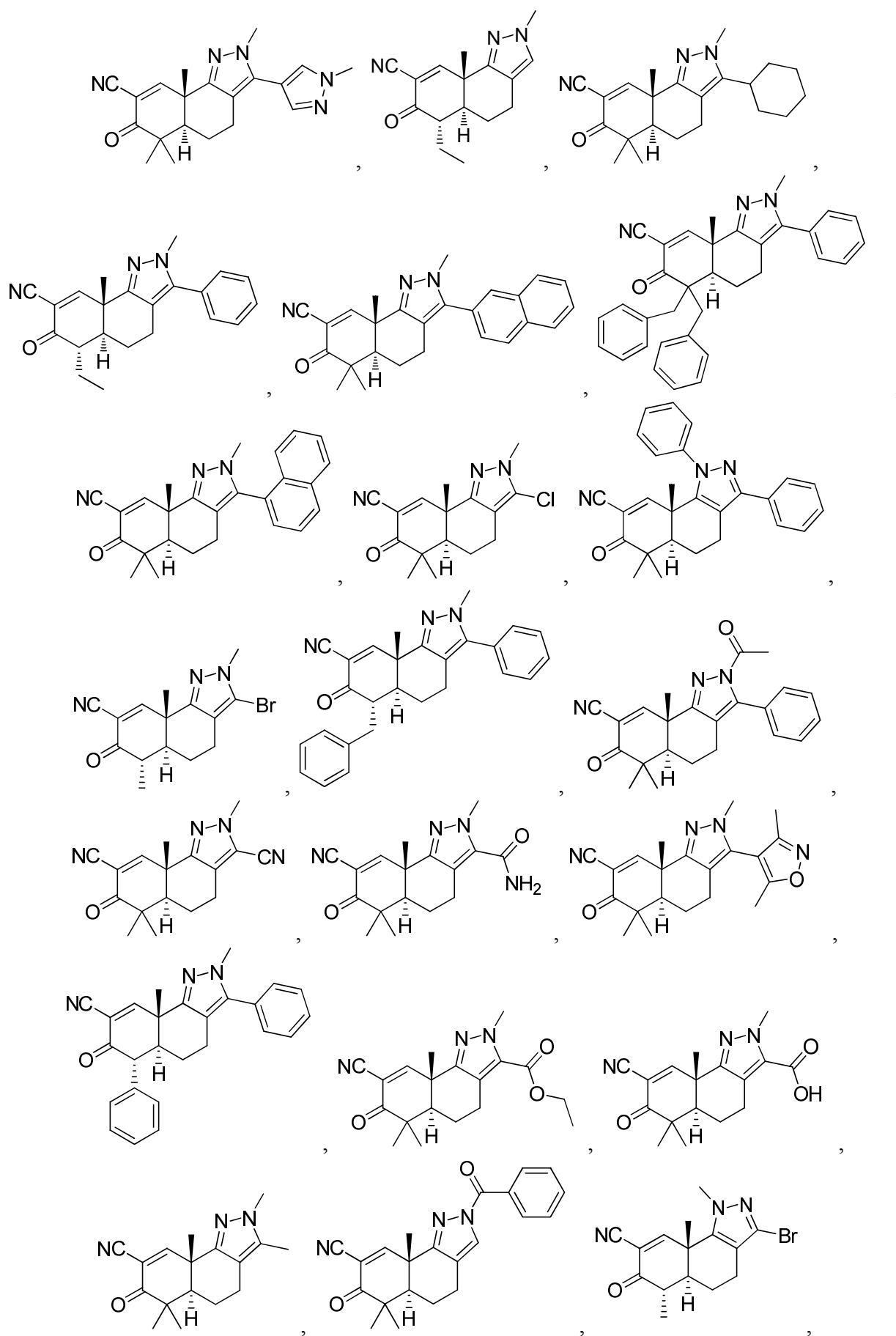
101. The compounds according to any one of claims 3-94, wherein carbon atom 10 is in the *S* configuration.

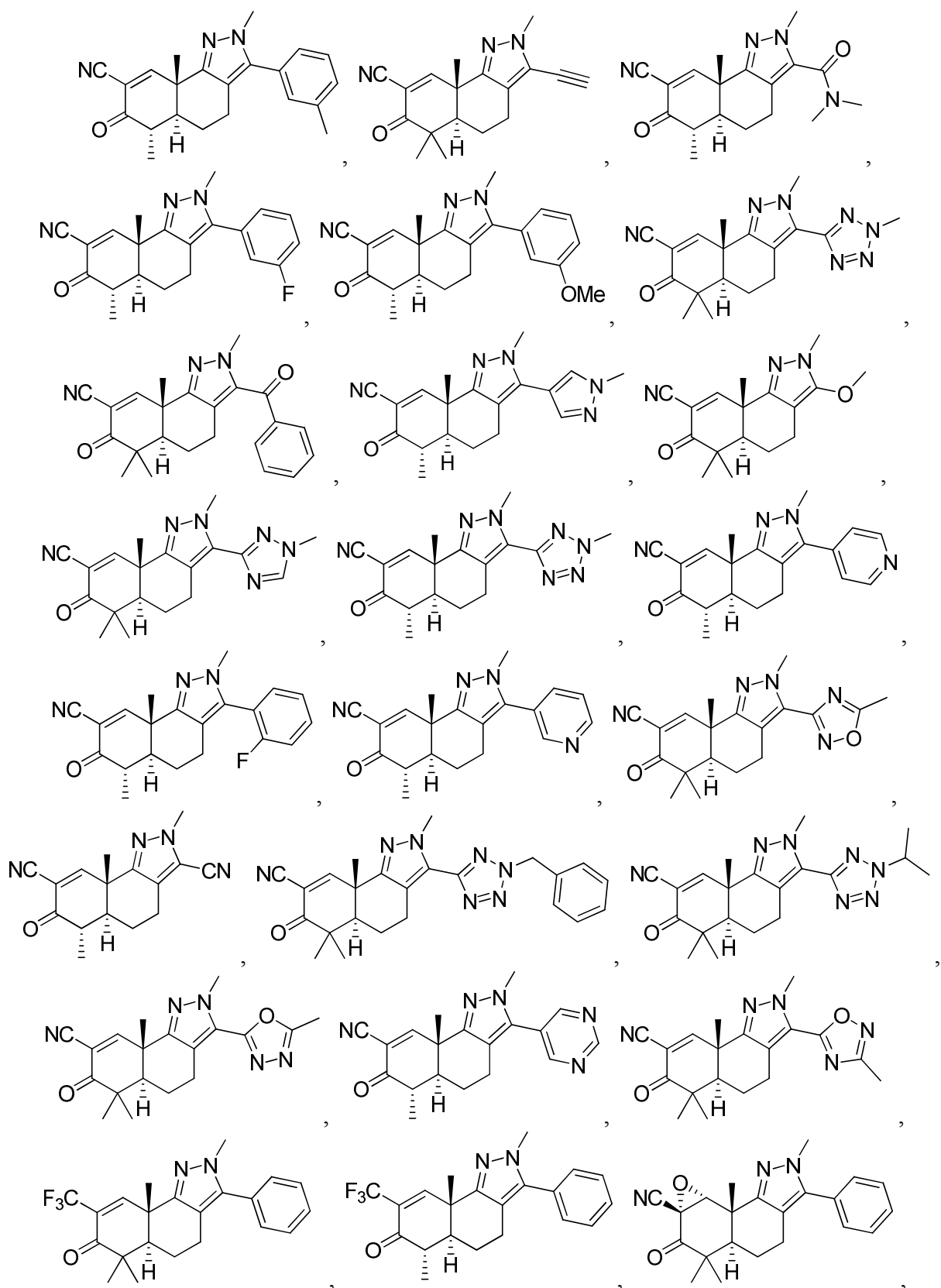
102. The compounds according to any one of claims 3-101, wherein carbon atom 5 is in the *R* configuration.

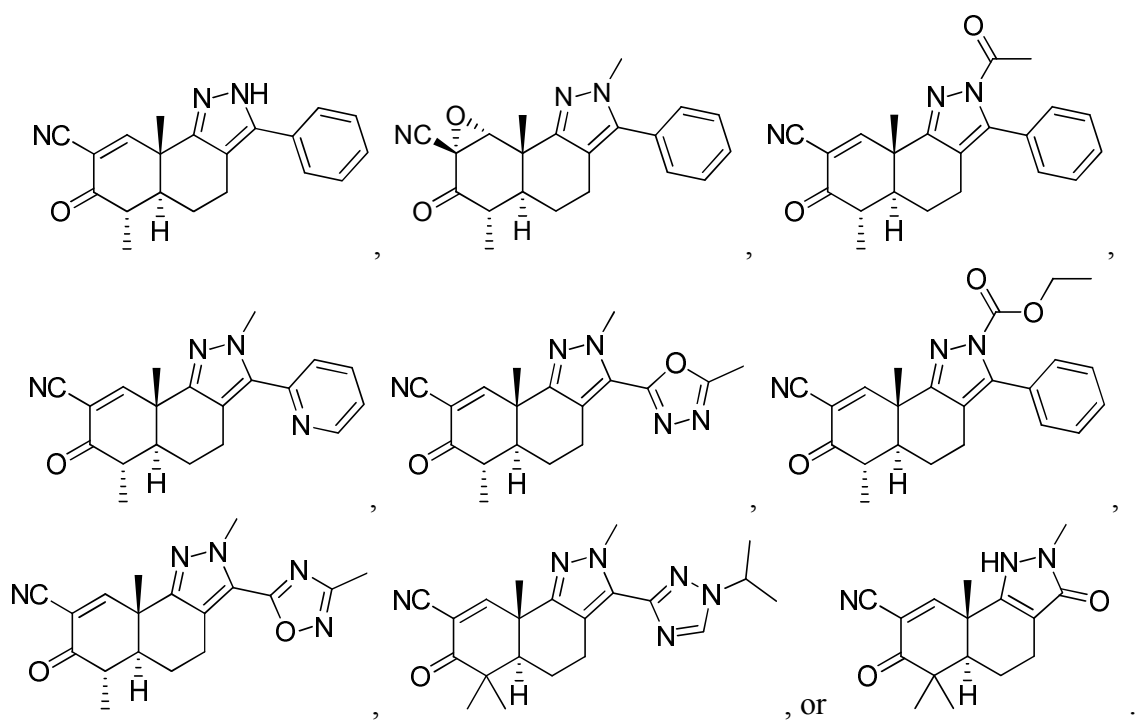
5 103. The compounds according to any one of claims 3-101, wherein carbon atom 5 is in the *S* configuration.

104. The compound of claim 1, further defined as:

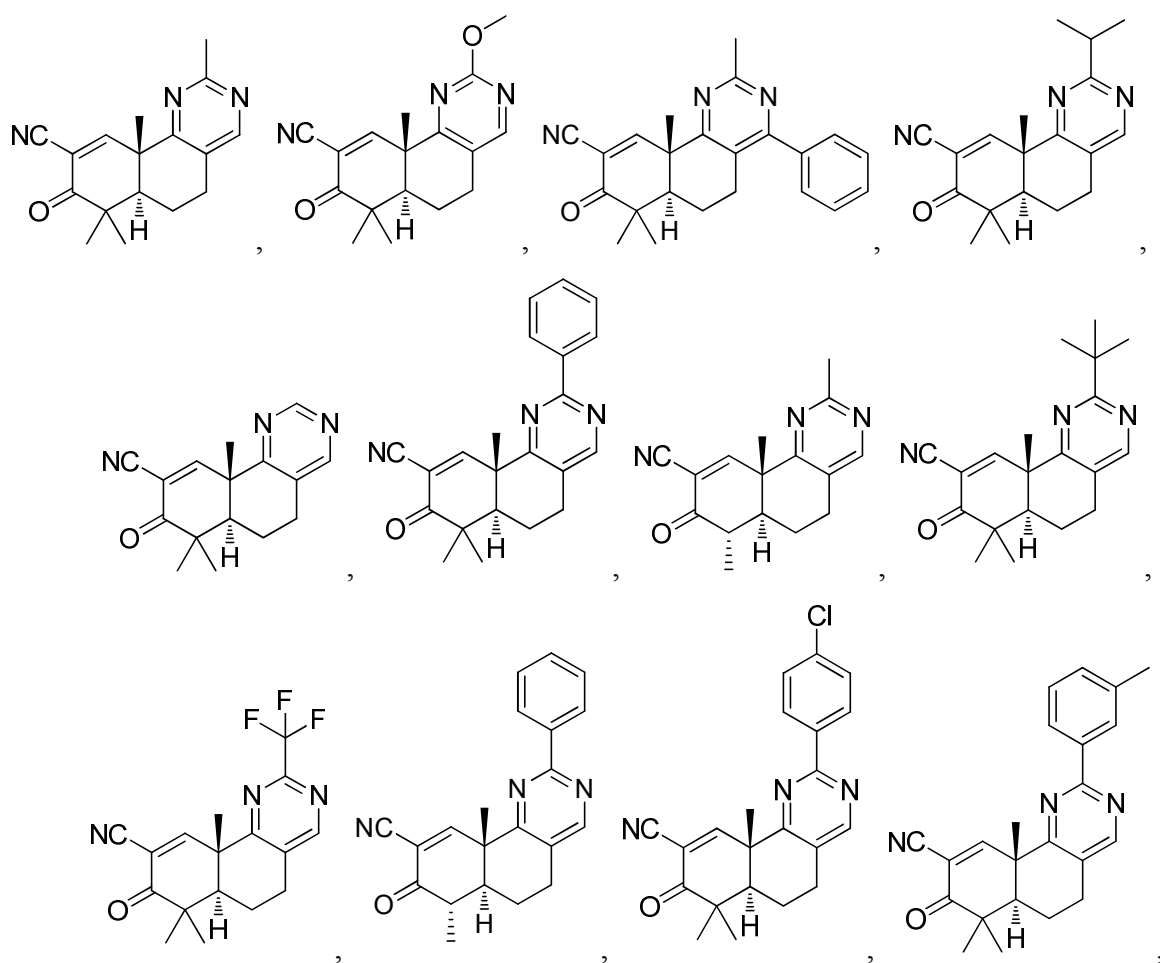


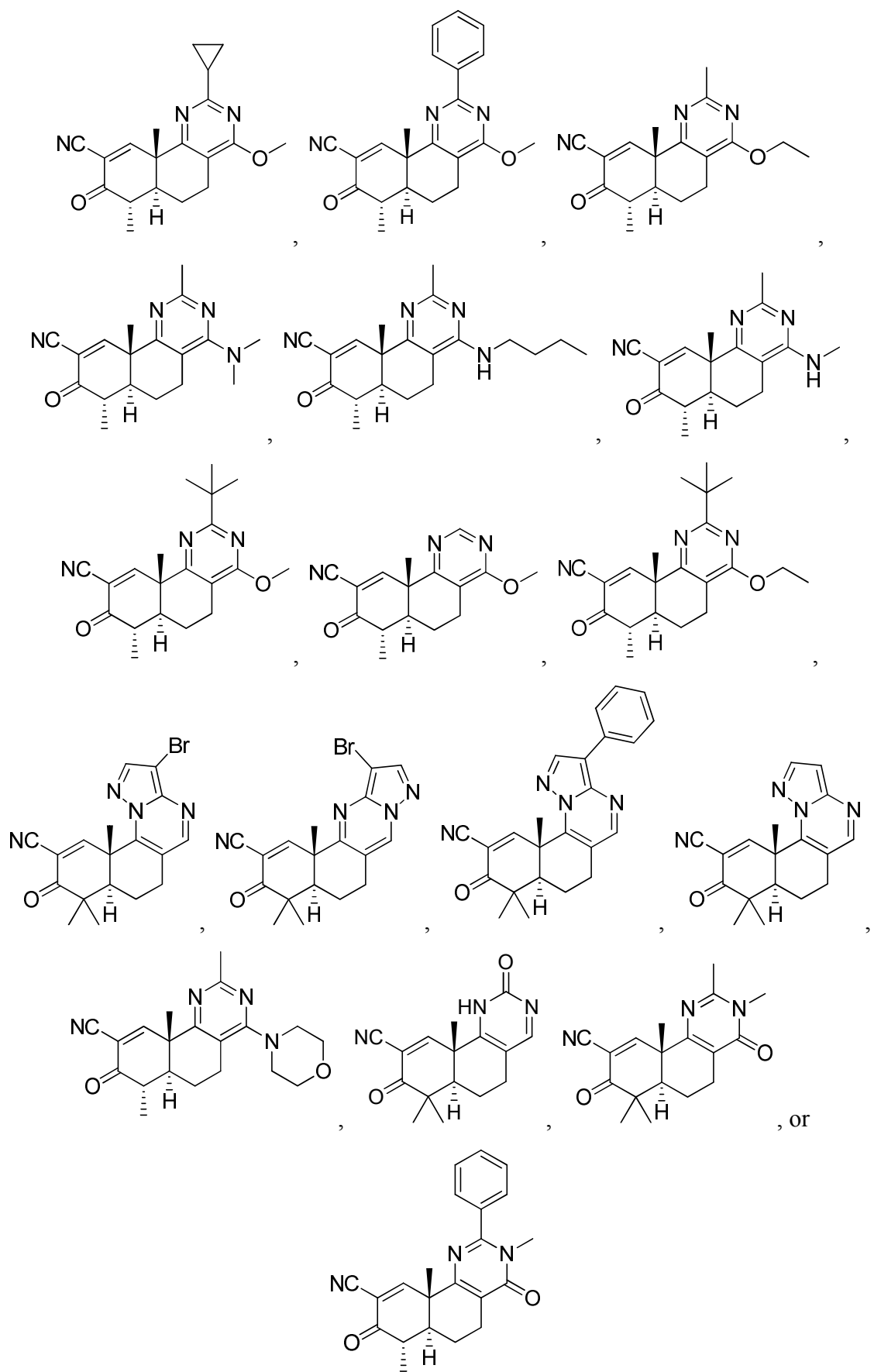




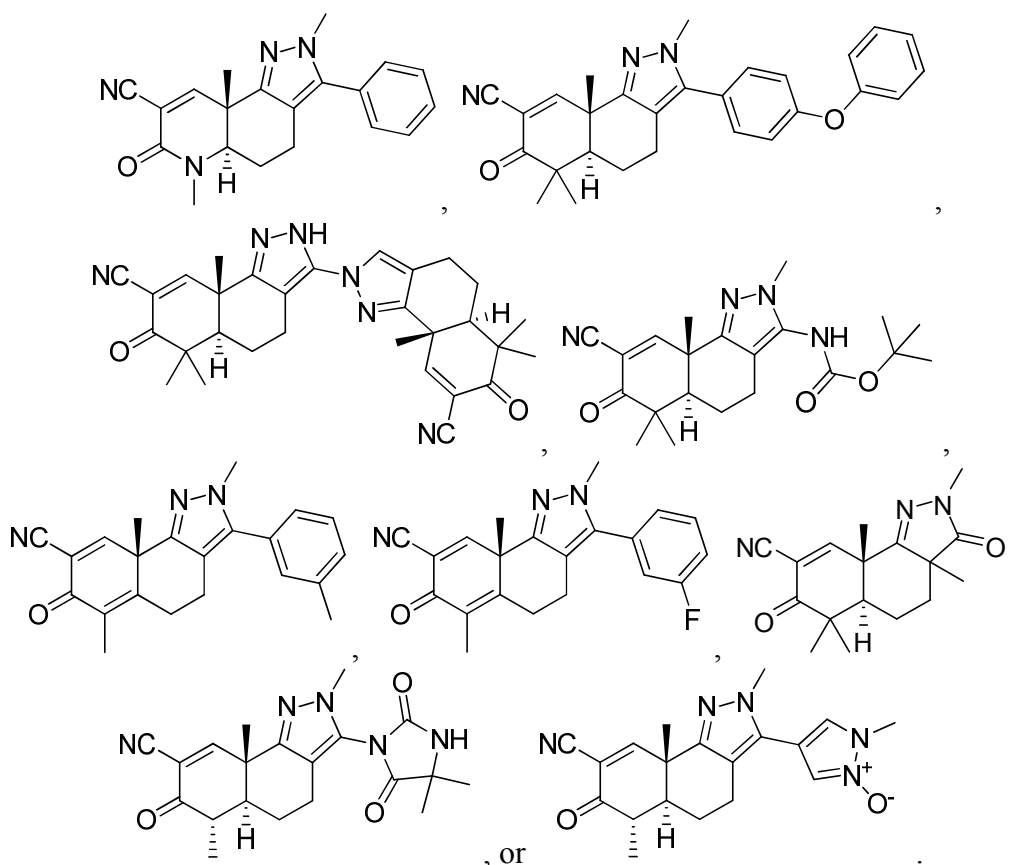


105. The compound of claim 1, further defined as:

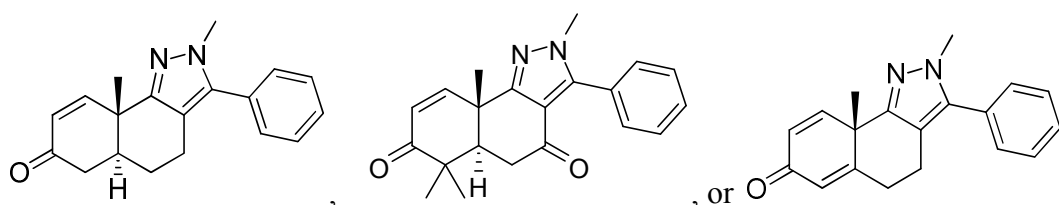




106. A compound of the formula:



107. A compound of the formula:



108. A pharmaceutical composition comprising:

a) the compound according to any one of claims 1-105;

10 b) an optical isomer of the compound, wherein the optical isomer is the enantiomer of the compound; and

c) an excipient.

109. The pharmaceutical composition of claim 108, wherein the ratio of the amount of compound to the amount of optical isomer is 1:1.

15 110. The pharmaceutical composition of claim 108, wherein the ratio of the amount of compound to the amount of optical isomer is 5:1.

111. The pharmaceutical composition of claim 108, wherein the ratio of the amount of compound to the amount of optical isomer is 10:1.
112. The pharmaceutical composition of claim 108, wherein the ratio of the amount of compound to the amount of optical isomer is 20:1.