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(56) Related Art
HONDA, T. et al, Journal of Organic Chemistry, 1998, vol. 63, pp. 4846-4849
RUZICKA, L. et al, Helvetica Chimica Acta, 1944, vol. 27, pp. 1185-1196
HONDA, T. et al, Journal of Medicinal Chemistry, 2000, vol. 43, 1866-1877
CHEUNG, H.T. et al, Phytochemistry, 1972, vol. 11, pp. 1771-17
JOHNS, S.R. et al, Australian Journal of Chemistry, 1983, vol. 36, pp. 2537-1547
PEAKMAN, T.M. et al, Tetrahedron, 1991, vol. 47, pp. 3779
WOLFF, G.A. et al, Tetrahedron, 1989, vol. 45, pp. 6721-6728

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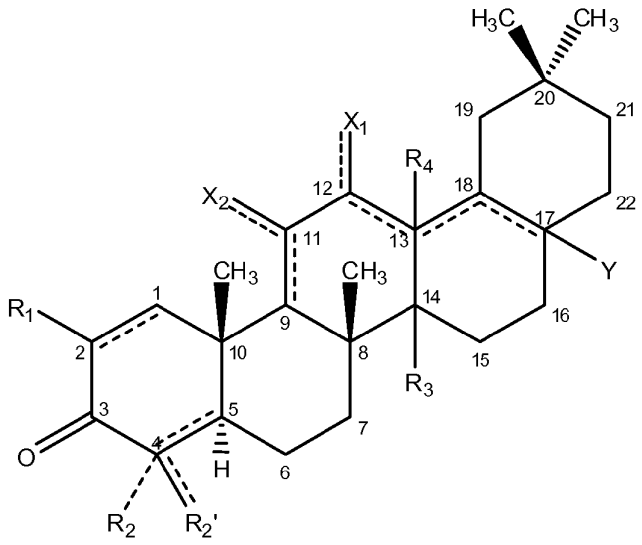
(54) Title: C4-MONOMETHYL TRITERPENOID DERIVATIVES AND METHODS OF USE THEREOF



(I),

(57) Abstract: Disclosed herein are novel C4-monomethyl triterpenoid compounds and derivatives thereof, including those of the formula (I) wherein the variables are defined herein. Also provided are pharmaceutical compositions, kits and articles of manufacture comprising such compounds. Methods and intermediates useful for making the compounds, and methods of using the compounds, for example as antioxidant inflammation modulators, and compositions thereof are also provided.

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GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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DESCRIPTION

C4-MONOMETHYL TRITERPENOID DERIVATIVES AND METHODS OF USE THEREOF

BACKGROUND OF THE INVENTION

The present application claims the benefit of priority to U.S. Provisional Application 61/452,017, filed March 11, 2011, the contents of which are incorporated herein by reference.

I. Field of the Invention

The present invention relates generally to the fields of biology and medicine. More particularly, it concerns compounds, compositions and methods for the treatment and prevention of diseases such as those associated with oxidative stress and inflammation.

II. Description of Related Art

The anti-inflammatory and anti-proliferative activity of the naturally occurring triterpenoid, oleanolic acid, has been improved by chemical modifications. For example, 2-cyano-3,12-diooxooleana-1,9(11)-dien-28-oic acid (CDDO) and related compounds have been developed (Honda *et al.,* 1997; Honda *et al.,* 1998; Honda *et al.,* 1999; Honda *et al.,* 2000a; Honda *et al.,* 2000b; Honda, *et al.,* 2002; Suh *et al.* 1998; Suh *et al.,* 1999; Place *et al.,* 2003; Liby *et al.,* 2005). The methyl ester, bardoxolone methyl (CDDO-Me), is currently being evaluated in phase III clinical trials for the treatment of diabetic nephropathy and chronic kidney disease.

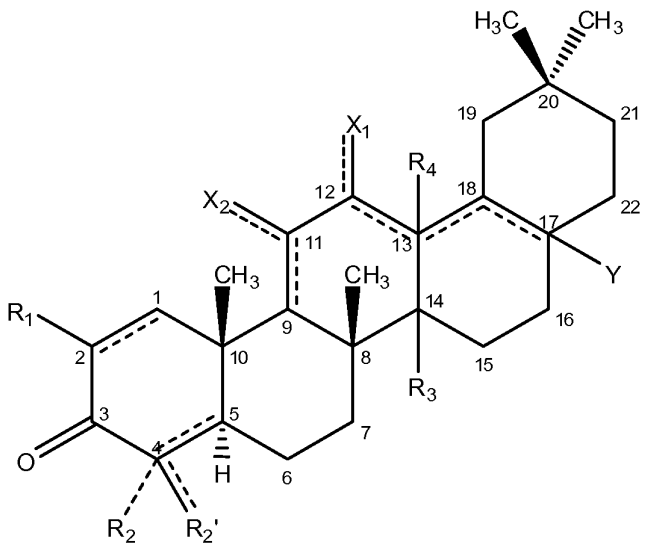
Synthetic triterpenoid analogs of oleanolic acid have also been shown to be inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda *et al.* (2000a); Honda *et al.* (2000b), and Honda *et al.* (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.*, 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). 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.

SUMMARY OF THE INVENTION

The present disclosure provides novel synthetic triterpenoid derivatives, with anti-inflammatory and/or antioxidant properties, pharmaceutical compositions, and methods for their manufacture, and methods for their use.

In one aspect, there are provided compounds of the formula:



(I),

wherein:

X_1 and X_2 are independently hydrogen, halo, hydroxy, amino or oxo, provided that X_1 is not oxo when carbon atoms 12 and 13 are connected to one another with a double bond, further provided that X_2 is not oxo when carbon atoms 9 and 11 are connected to one another with a double bond;

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$;

R_2 is hydrogen or R_2 is absent when the atom to which it is bound forms part of a double bond;

R_2' is hydrogen, $=CH_2$, $alkyl_{(C\leq 8)}$, or substituted $alkyl_{(C\leq 8)}$;

R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_c; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$,

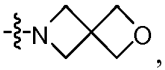
acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, alkylthio$_{(C\leq 8)}$, acylthio$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or substituted versions of any of these groups;

−alkanediyl$_{(C\leq 8)}$−R_b, −alkenediyl$_{(C\leq 8)}$−R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

heteroaryl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −OC(O)NH−alkyl$_{(C\leq 8)}$, −OC(O)CH_2NHC(O)O−*t*-butyl, −OCH_2−alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups;

−$(CH_2)_m$C(O)R_c, wherein m is 0–6 and R_c is:

hydrogen, hydroxy, halo, amino, −NHOH,  , or thio; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −NH−alkoxy$_{(C\leq 8)}$, −NH−heterocycloalkyl$_{(C\leq 8)}$, −NHC(NOH)−alkyl$_{(C\leq 8)}$, −NH−amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_c and R_3, taken together, are −O− or −NR_d−, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

R_c and R_4, taken together, are −O− or −NR_d−, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

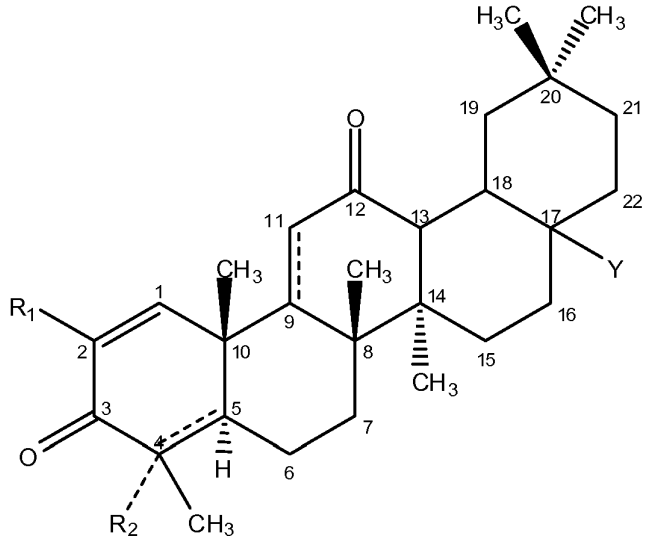
−NHC(O)R_e, wherein R_e is:

hydrogen, hydroxy, amino; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(II),

wherein:

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$;

R_2 is hydrogen or R_2 is absent when the atom to which it is bound forms part of a double bond; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

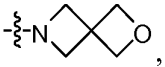
$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

−alkanediyl$_{(C\leq 8)}$−R_b, −alkenediyl$_{(C\leq 8)}$−R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

heteroaryl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −OC(O)NH−alkyl$_{(C\leq 8)}$, −OC(O)CH_2NHC(O)O−*t*-butyl, −OCH_2−alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups;

−$(CH_2)_m$C(O)R_c, wherein m is 0–6 and R_c is:

hydrogen, hydroxy, halo, amino, −NHOH,  , or thio; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −NH−alkoxy$_{(C\leq 8)}$, −NH−heterocycloalkyl$_{(C\leq 8)}$, −NHC(NOH)−alkyl$_{(C\leq 8)}$, −NH−amido$_{(C\leq 8)}$, or a substituted version of any of these groups; or

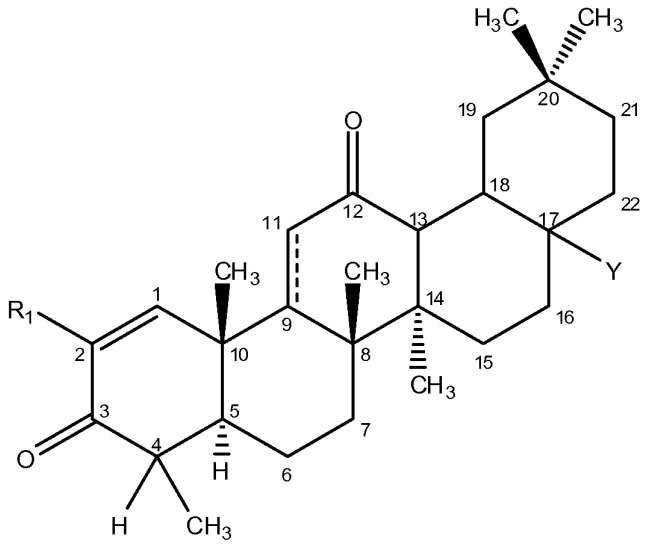
−NHC(O)R_e, wherein R_e is:

hydrogen, hydroxy, amino; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(III),

wherein:

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

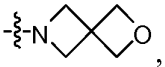
$-alkanediyl_{(C\leq 8)}-R_b$, $-alkenediyl_{(C\leq 8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

$heteroaryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $-OC(O)NH-alkyl_{(C\leq 8)}$, $-OC(O)CH_2NHC(O)O-t$-butyl,

$-OCH_2-alkylthio_{(C\leq 8)}$, or a substituted version of any of these groups;

$-(CH_2)_mC(O)R_c$, wherein m is 0–6 and R_c is:

hydrogen, hydroxy, halo, amino, –NHOH,  , or thio; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $-NH-alkoxy_{(C\leq 8)}$, $-NH-heterocycloalkyl_{(C\leq 8)}$, $-NHC(NOH)-alkyl_{(C\leq 8)}$, $-NH-amido_{(C\leq 8)}$, or a substituted version of any of these groups; or

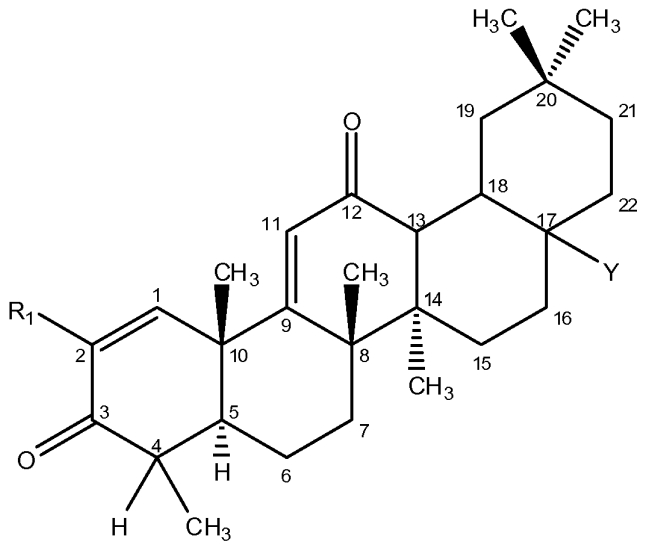
$-NHC(O)R_e$, wherein R_e is:

hydrogen, hydroxy, amino; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(IV),

wherein:

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

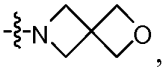
$-alkanediyl_{(C\leq 8)}-R_b$, $-alkenediyl_{(C\leq 8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or thio; or

$heteroaryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $-OC(O)NH-alkyl_{(C\leq 8)}$, $-OC(O)CH_2NHC(O)O-t$-butyl,

$-OCH_2-alkylthio_{(C\leq 8)}$, or a substituted version of any of these groups;

$-(CH_2)_mC(O)R_c$, wherein m is 0–6 and R_c is:

hydrogen, hydroxy, halo, amino, –NHOH,  , or thio; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $-NH-alkoxy_{(C\leq 8)}$, $-NH-heterocycloalkyl_{(C\leq 8)}$, $-NHC(NOH)-alkyl_{(C\leq 8)}$, $-NH-amido_{(C\leq 8)}$, or a substituted version of any of these groups; or

$-NHC(O)R_e$, wherein R_e is:

hydrogen, hydroxy, amino; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

In some embodiments, the compounds the bond between carbon atoms 1 and 2 is a double bond. In some embodiments, the bond between carbon atoms 1 and 2 is a single bond. In some embodiments, the bond between carbon atoms 4 and 5 is a single bond. In some embodiments, the bond between carbon atoms 4 and 5 is a double bond. In some embodiments, the bond between carbon atoms 9 and 11 is a double bond.

In some embodiments, the bond between carbon atoms 9 and 11 is a single bond.

In some embodiments, X_1 is oxo. In some embodiments, X_1 is hydrogen. In some embodiments, X_1 is hydroxy. In some embodiments, X_2 is oxo. In some embodiments, X_2 is hydrogen.

In some embodiments, R_1 is −CN. In some embodiments, R_1 is $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$. In some embodiments, R_a is −OH. In some embodiments, R_a is $alkoxy_{(C1-4)}$. In some embodiments, R_a is methoxy. In some embodiments, R_a is $-NH_2$. In some embodiments, R_1 is −H. In some embodiments, R_1 is halo. In some embodiments, R_1 is iodo.

In some embodiments, R_2 is hydrogen. In some embodiments, R_2 is absent. In some embodiments, R_2' is $alkyl_{(C\leq 8)}$. In some embodiments, R_2' is methyl. In some embodiments, R_2' is hydrogen. In some embodiments, R_2' is $=CH_2$.

In some embodiments, R_3 is methyl. In some embodiments, R_3 is hydrogen. In some embodiments, R_4 is hydrogen. In some embodiments, R_4 is methyl. In some embodiments, R_4 is hydroxy.

In some embodiments, Y is $-(CH_2)_mC(O)R_c$, wherein m is 0–6 and R_c is hydrogen, hydroxy, amino, −NHOH, $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $-NH-alkoxy_{(C\leq 8)}$, $-NH-heterocycloalkyl_{(C\leq 8)}$, $-NHC(NOH)-alkyl_{(C\leq 8)}$, $-NH-amido_{(C\leq 8)}$, or a substituted version of any of these groups other than hydrogen, hydroxy, amino, and –NHOH.

In some embodiments, R_c is $alkoxy_{(C\leq 8)}$. In some embodiments, R_c is methoxy, ethoxy or isopropoxy. In some embodiments, R_c is hydroxy. In some embodiments, R_c is amino. In some embodiments, R_c is $alkylamino_{(C\leq 8)}$ or substituted $alkylamino_{(C\leq 8)}$. In some embodiments, R_c is methylamino, ethylamino, *n*-butylamino or 2,2,2-trifluoroethylamino. In some embodiments, R_c is $heteroaryl_{(C\leq 8)}$. In some embodiments, R_c is imidazolyl or dimethylimidazolyl. In some embodiments, R_c is –NHOH or $-NHOCH_3$. In some embodiments, R_c is $heterocycloalkyl_{(C\leq 8)}$ or substituted $heterocycloalkyl_{(C\leq 8)}$. In some embodiments, R_c is *N*-pyrrolidinyl, *N*-morpholinyl, *N*-piperidinyl or *N*-azetidinyl. In some embodiments, R_c is $-NH-heterocycloalkyl_{(C\leq 8)}$. In some embodiments, R_c is $-NH-amido_{(C\leq 8)}$ or a

substituted version thereof. In some embodiments, R_c is $-NHNHC(O)H$, $-NHNHC(O)CH_3$ or $-NHNHC(O)CH_2OCH_3$. In some embodiments, R_c is $-NHC(NOH)CH_3$. In some embodiments, m is 0. In some embodiments, m is 2.

In some embodiments, Y is $-alkanediyl_{(C\leq 8)}-R_b$. In some embodiments, Y is $-CH_2-R_b$. In some embodiments, R_b is hydroxy. In some embodiments, R_b is $acyloxy_{(C\leq 8)}$ or substituted $acyloxy_{(C\leq 8)}$. In some embodiments, R_b is acetyloxy, or trifluoroacetyloxy, $-OC(O)CH_2NH_2$. In some embodiments, R_b is $alkoxy_{(C\leq 8)}$ or substituted $alkoxy_{(C\leq 8)}$. In some embodiments, R_b is methoxy or fluoromethoxy. In some embodiments, R_b is $heteroaryl_{(C\leq 8)}$. In some embodiments, R_b is $-OC(O)NH-alkyl_{(C\leq 8)}$, $-OC(O)CH_2NHC(O)O-t$-butyl, or $-OCH_2-alkylthio_{(C\leq 8)}$.

In some embodiments, Y is $-CN$. In some embodiments, Y is isocyanate. In some embodiments, Y is fluoro. In some embodiments, Y is $alkylsulfonylamino_{(C\leq 8)}$ or substituted $alkylsulfonylamino_{(C\leq 8)}$. In some embodiments, Y is $-NHS(O)_2CH_3$ or $-NHS(O)_2CH_2CF_3$. In some embodiments, Y is $heteroaryl_{(C\leq 8)}$. In some embodiments, Y is oxadiazolyl, methyloxadiazolyl, or methoxymethyloxadiazolyl. In other embodiments, Y is $amido_{(C\leq 8)}$, $acyl_{(C\leq 8)}$ or substituted versions of either group.

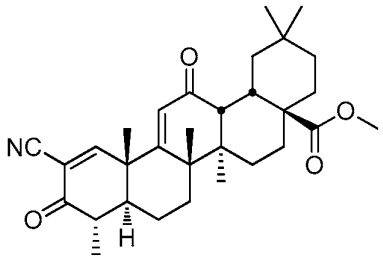
In some embodiments, Y is $-NHC(O)R_e$, wherein R_e is hydrogen, hydroxy, amino, $alkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, or substituted version of any of these groups other than hydrogen, hydroxy and amino. In some embodiments, R_e is hydrogen. In some embodiments, R_e is amino. In some embodiments, R_e is $alkyl_{(C\leq 8)}$ or substituted $alkyl_{(C\leq 8)}$. In some embodiments, R_e is methyl, ethyl, cyclopropyl, cyclobutyl, *n*-hexyl, 1,1-difluoroethyl, or 2,2,2-trifluoroethyl. In some embodiments, R_e is $aryl_{(C\leq 8)}$. In some embodiments, R_e is $alkoxy_{(C\leq 8)}$. In some embodiments, R_e is methoxy, ethoxy, or isopropoxy. In some embodiments, R_e is $alkylamino_{(C\leq 8)}$ or $dialkylamino_{(C\leq 8)}$. In some embodiments, R_e is methylamino, ethylamino, or dimethylamino.

In some embodiments, Y is $-(CH_2)_mC(O)R_c$, wherein m is 0 and wherein R_c and R_3 are taken together and are $-O-$. In some embodiments, Y is $-(CH_2)_mC(O)R_c$, wherein m is 0 and wherein R_c and R_4 are taken together and are $-O-$.

In embodiments having a hydrogen at carbon atom 13, the hydrogen is in the beta orientation. In others it is the alpha orientation. In some embodiments, the hydrogen at carbon atom 18 is in the beta orientation; in other embodiments, it is in

the alpha orientation. For example, in some embodiments, there are hydrogen atoms at both carbon atoms 13 and 18, and they are both in the beta orientations.

In some embodiments, the invention provides compounds of the formulas:



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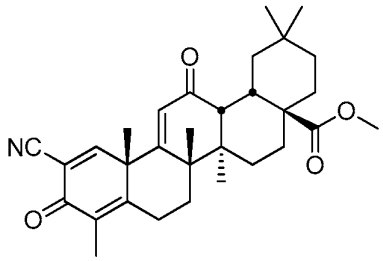

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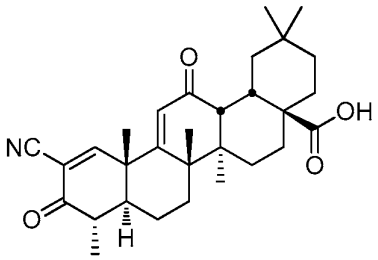

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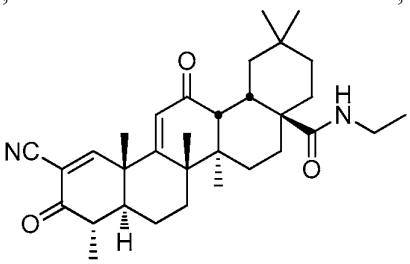

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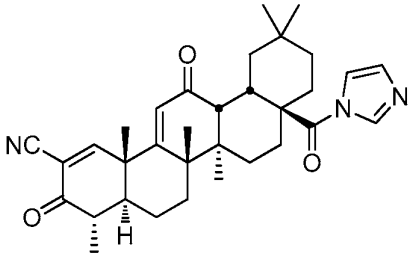

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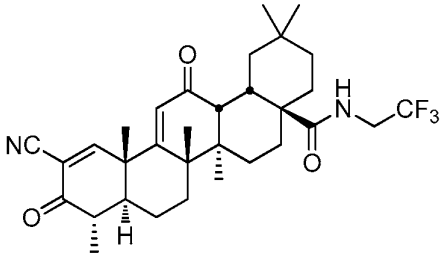

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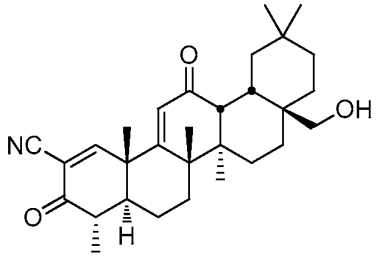

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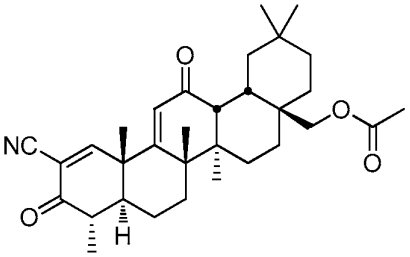

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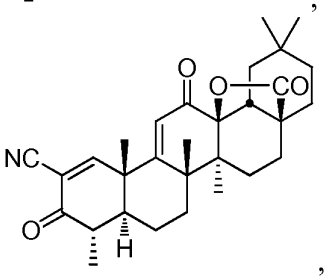

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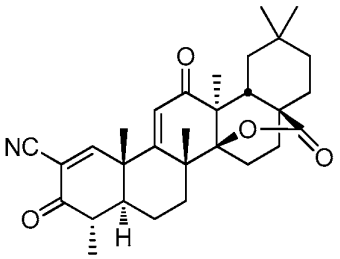

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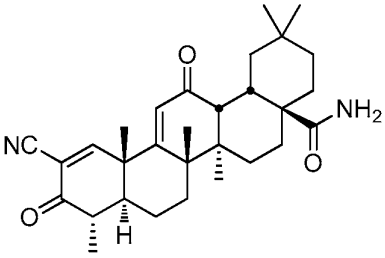

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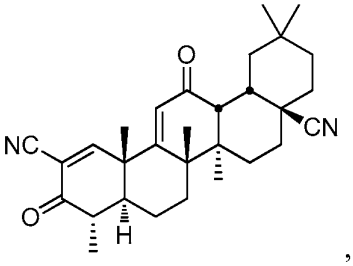

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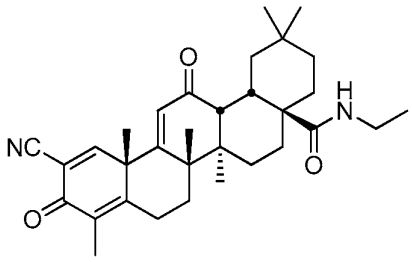
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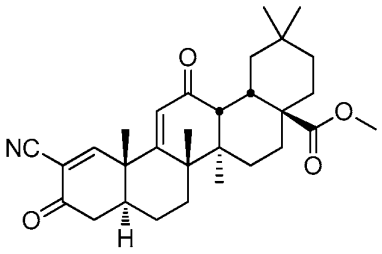
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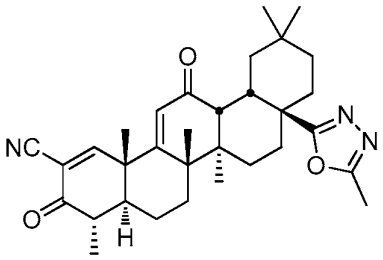
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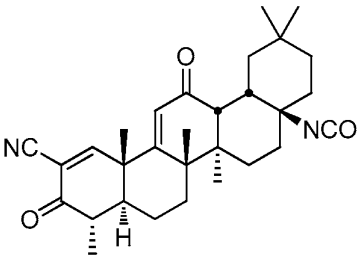
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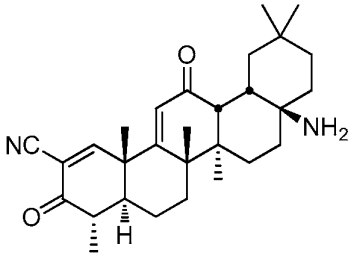
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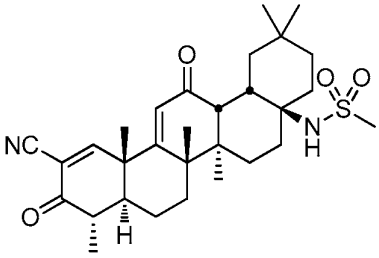
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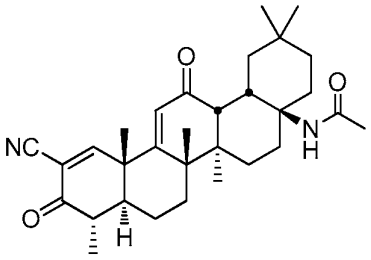
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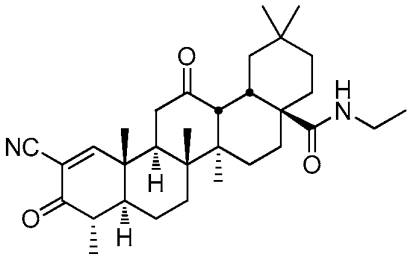
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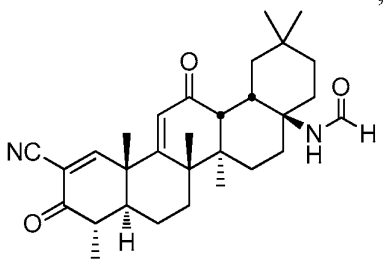
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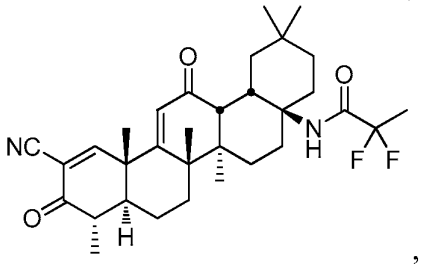
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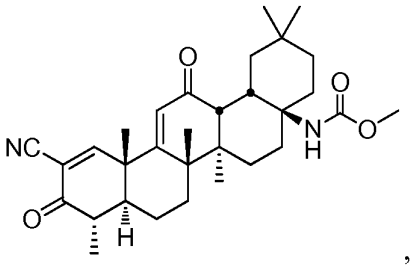
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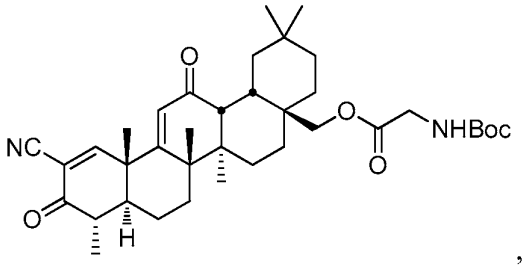
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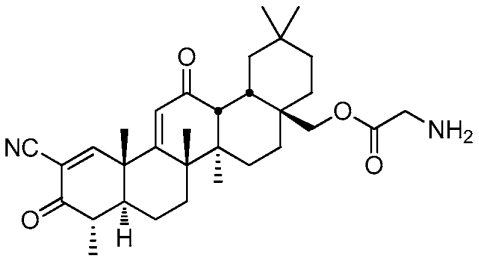
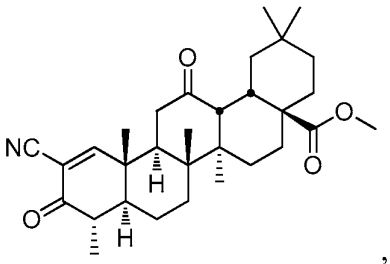
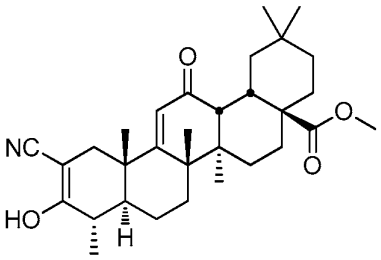
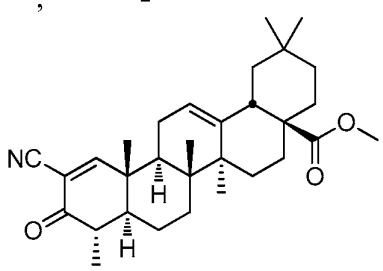
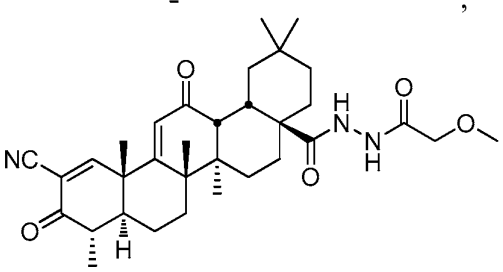
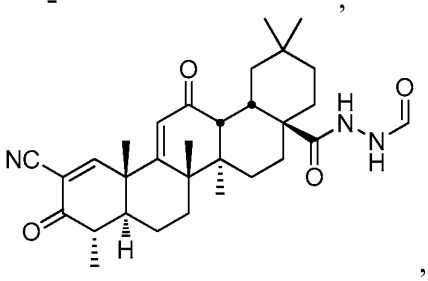
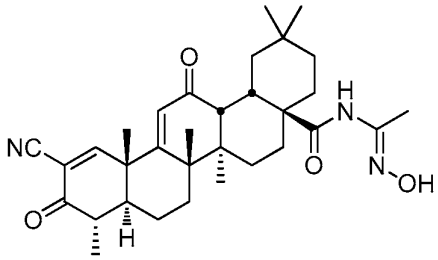
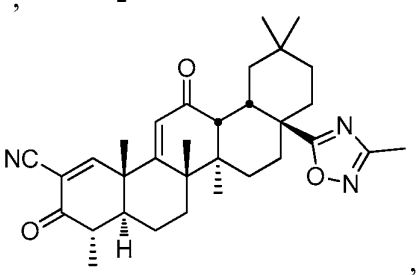
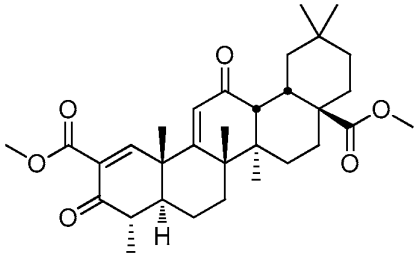
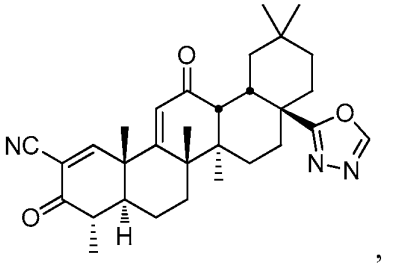
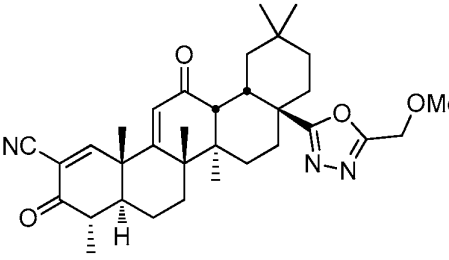
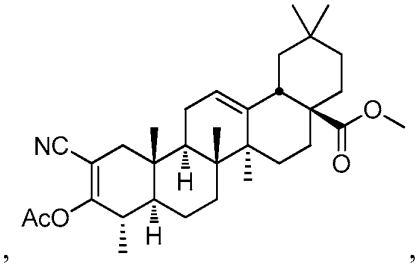


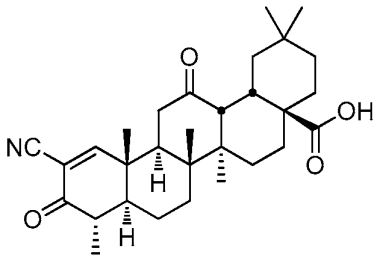
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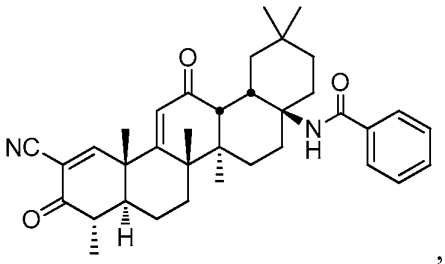
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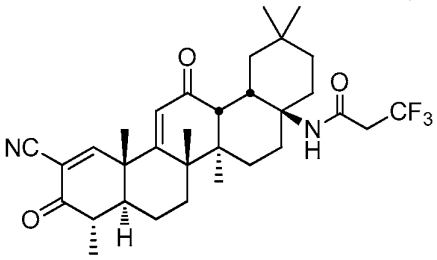
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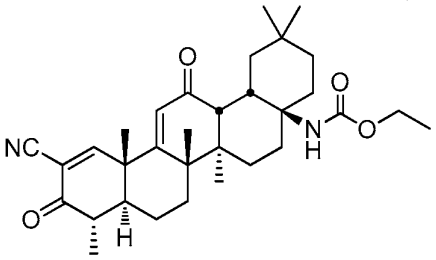
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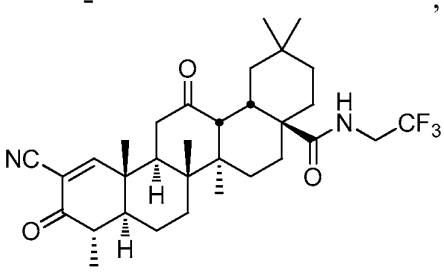
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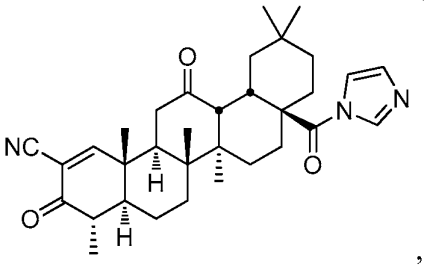
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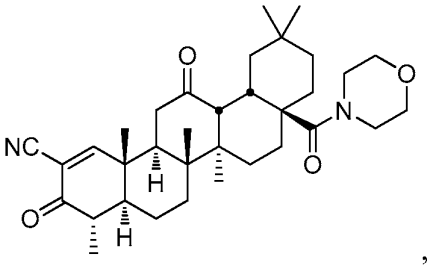
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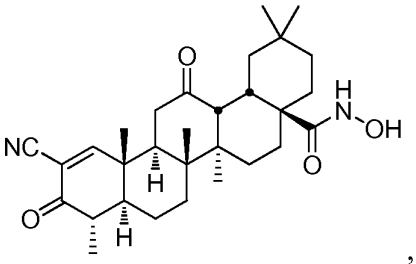
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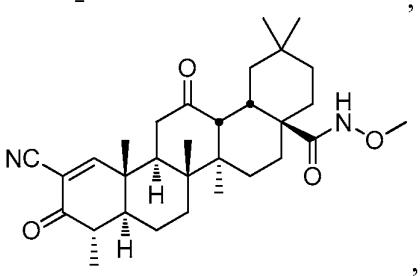
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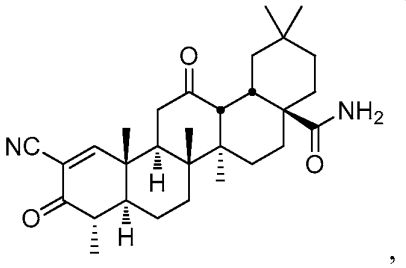
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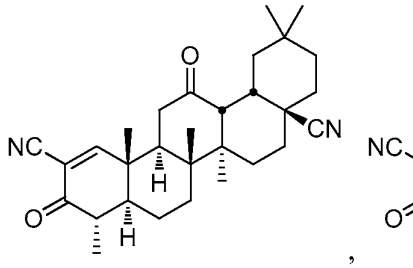
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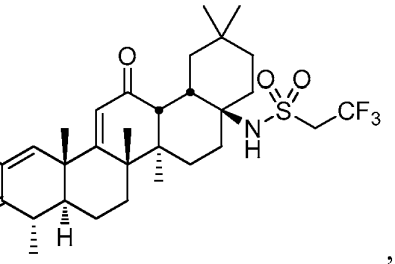
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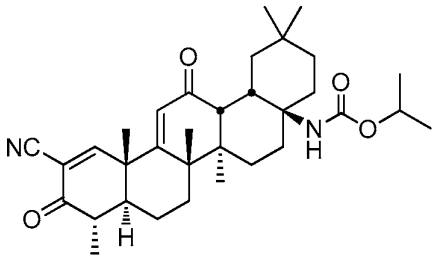
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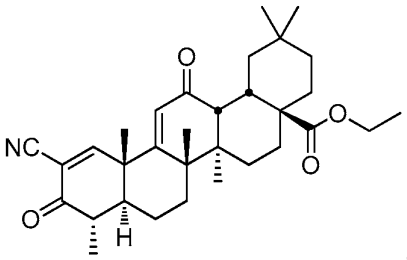
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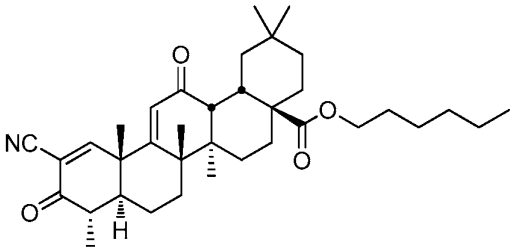
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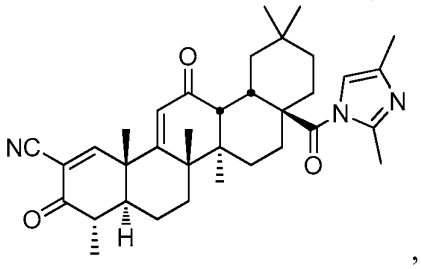
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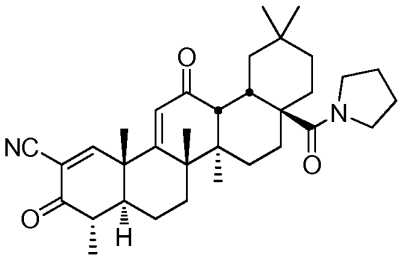
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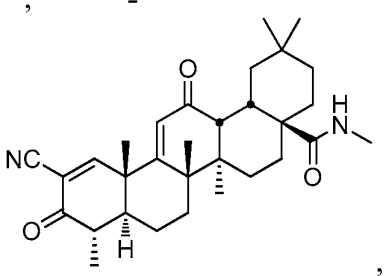
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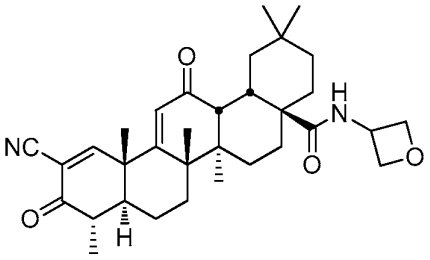
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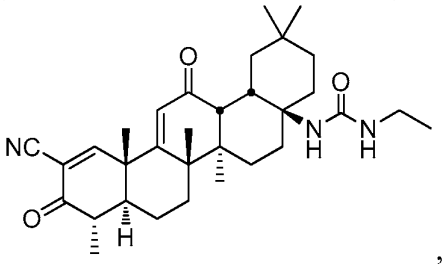
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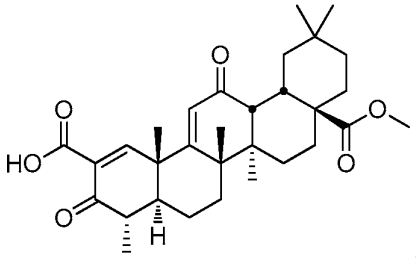
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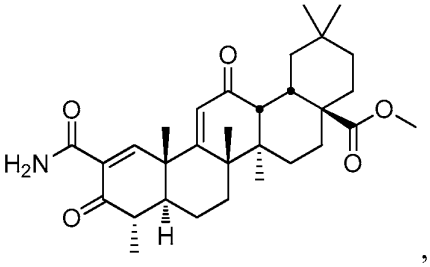
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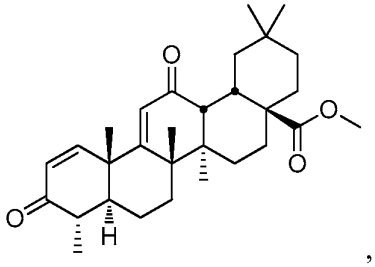
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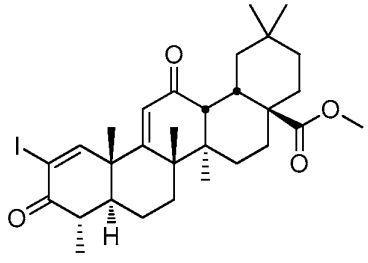
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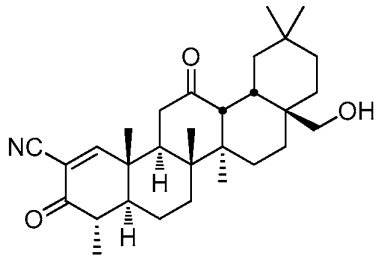
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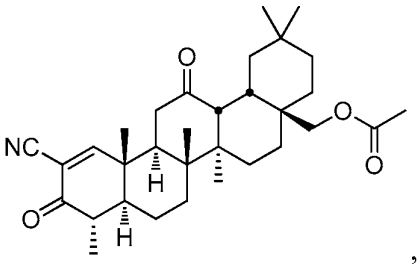
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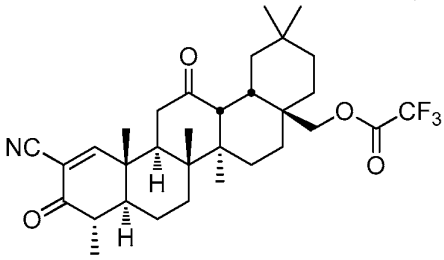
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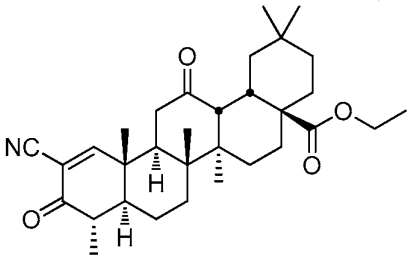
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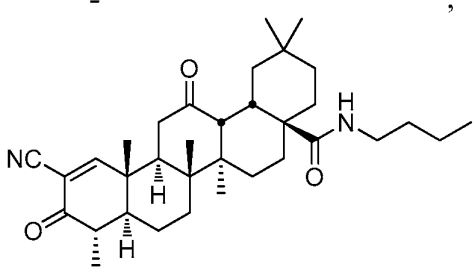
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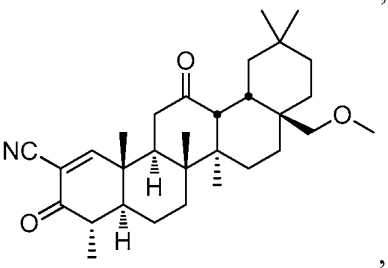
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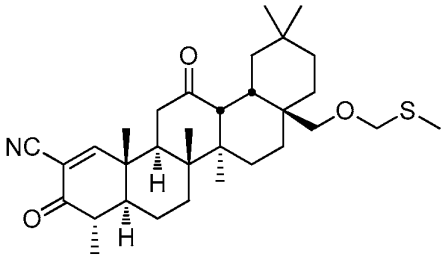
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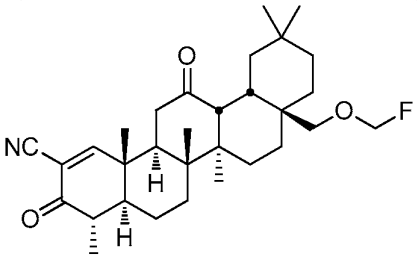
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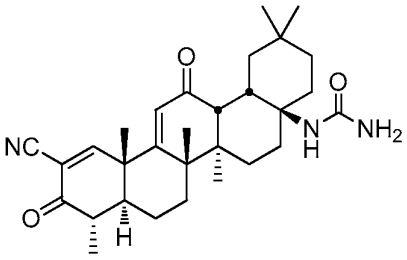
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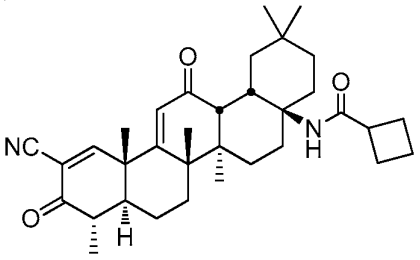
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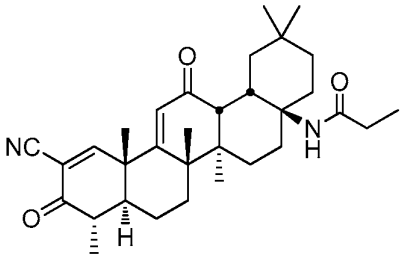
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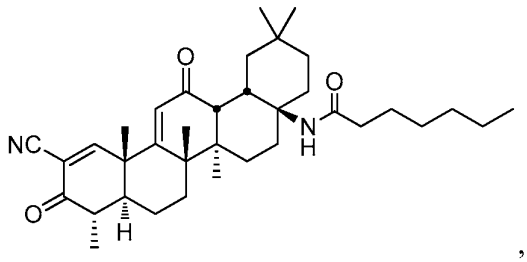
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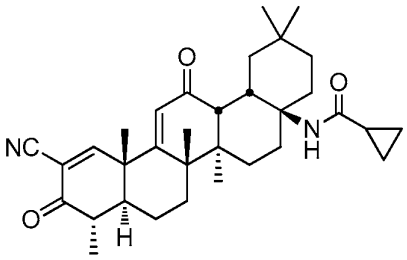
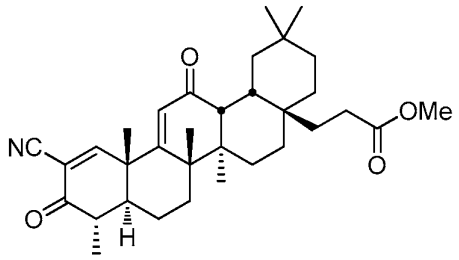
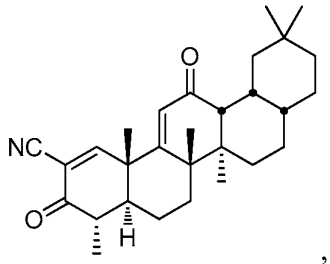
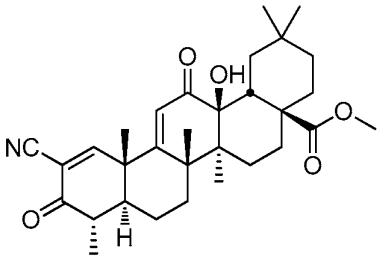
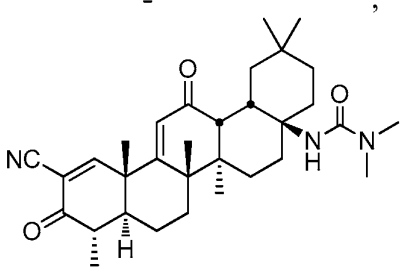
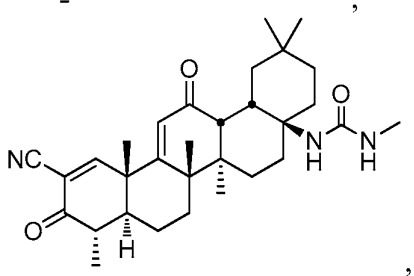
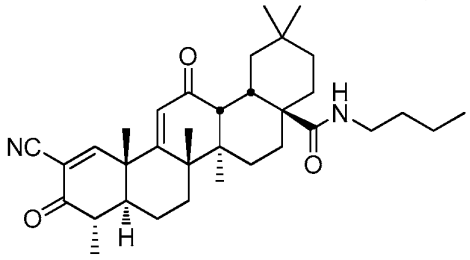
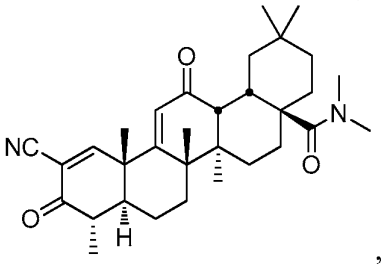
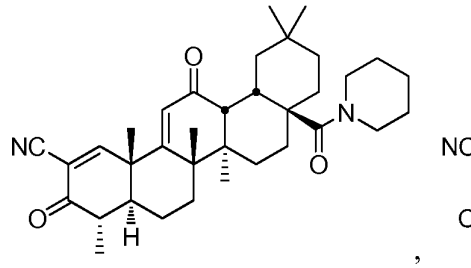
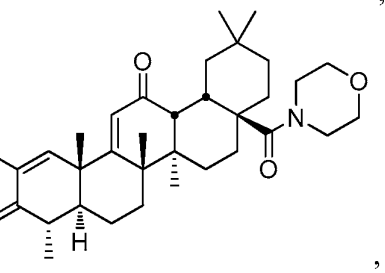
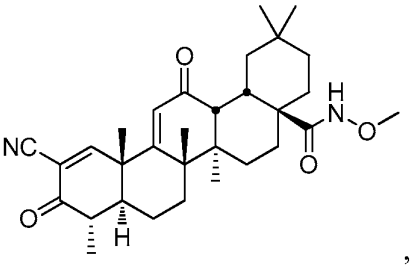
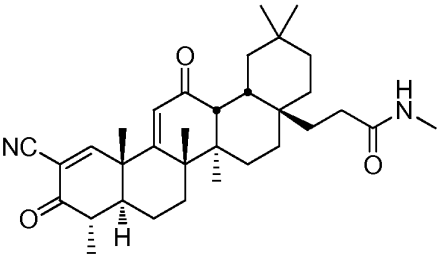

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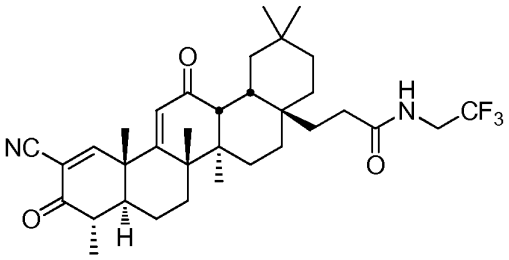
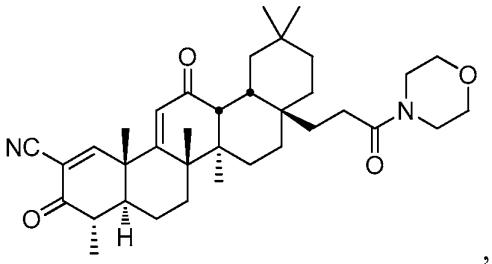
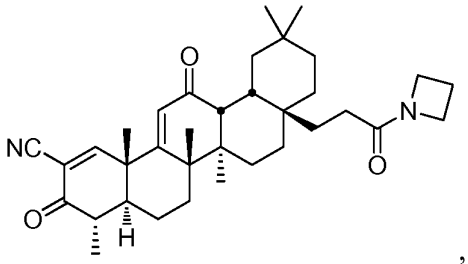
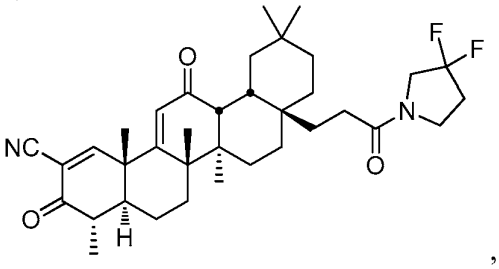
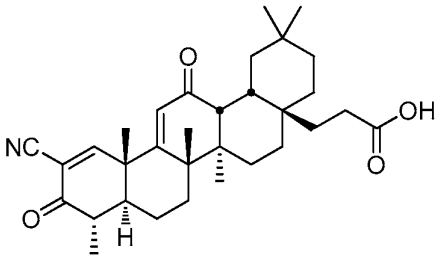
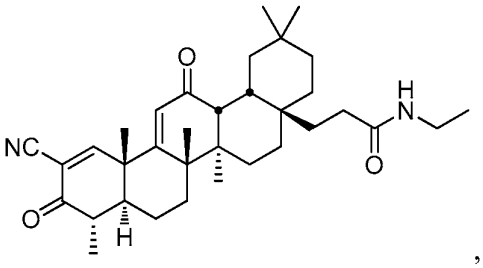
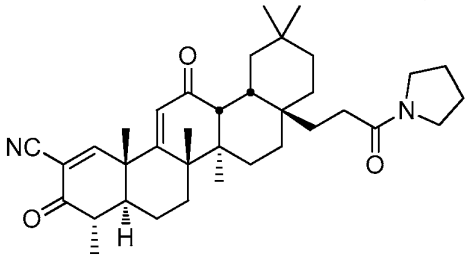
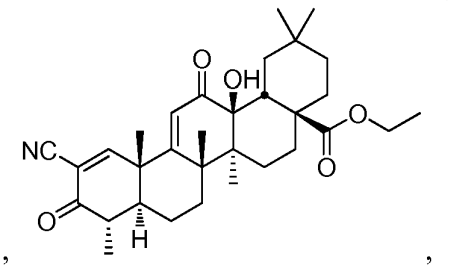
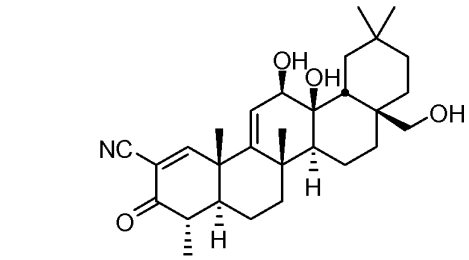
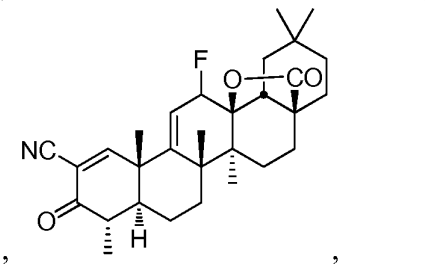

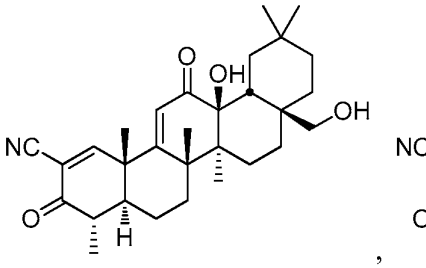
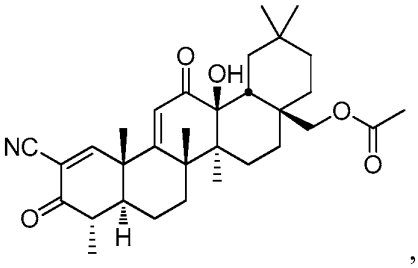

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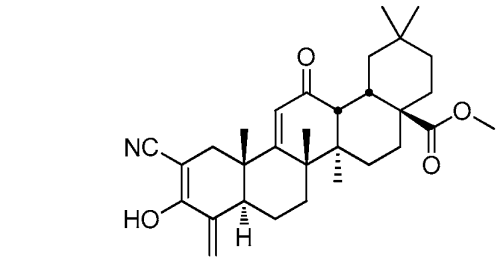
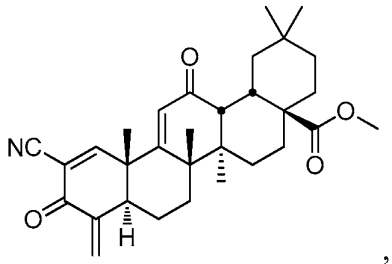
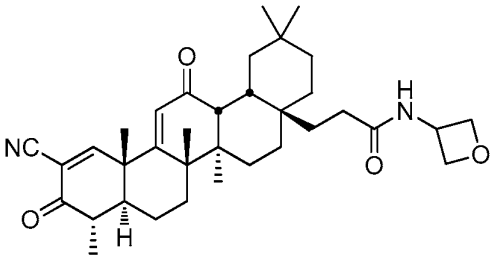
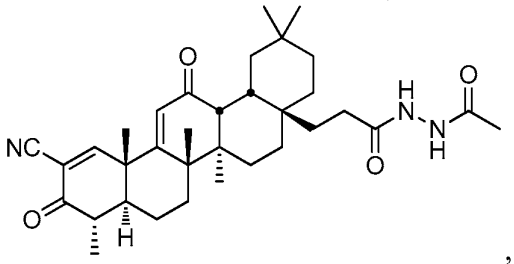
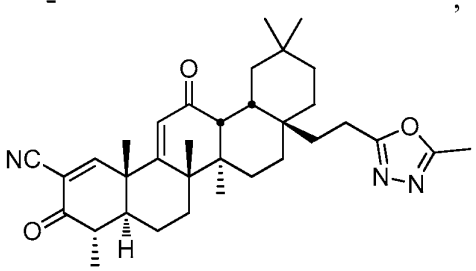
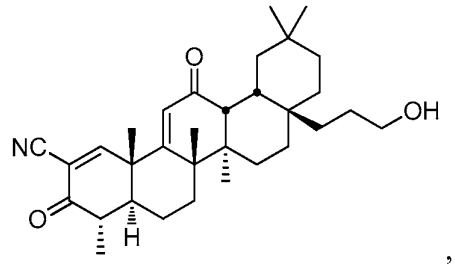
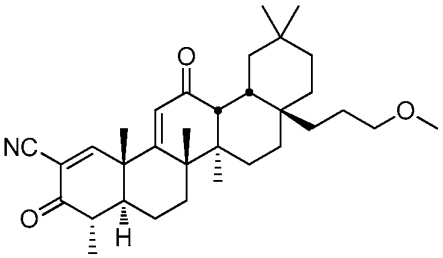
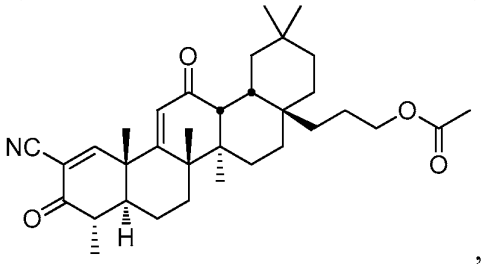
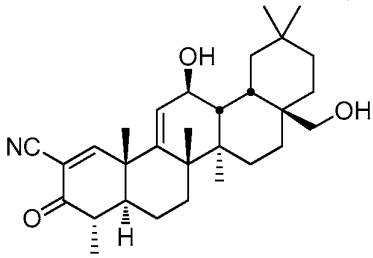
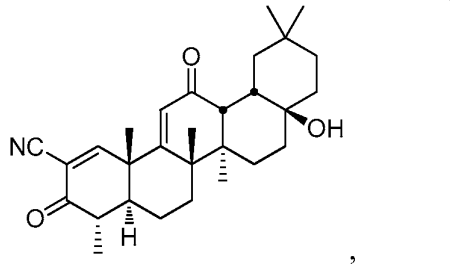
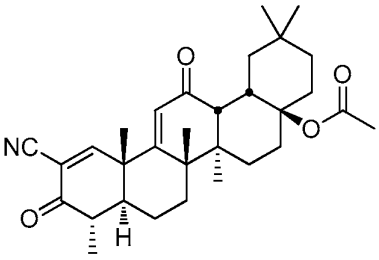
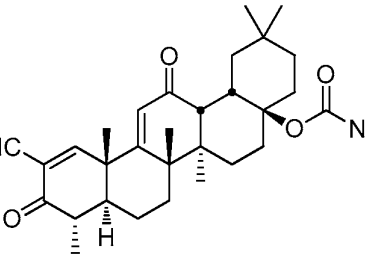
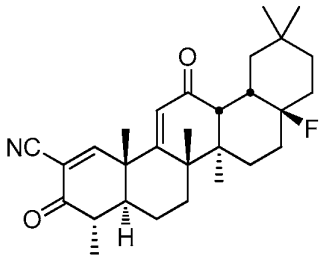
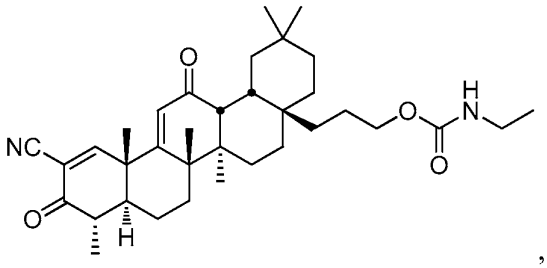
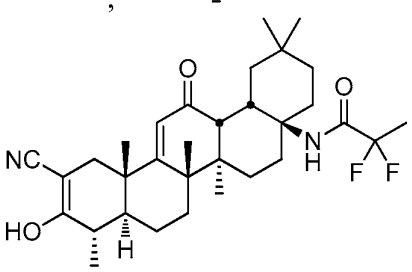
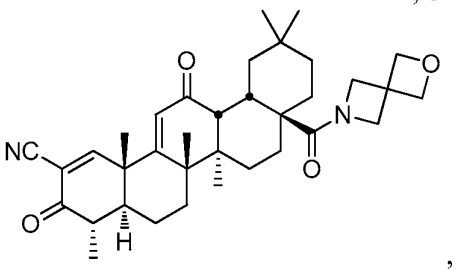













and pharmaceutically acceptable salts and tautomers thereof.

In some aspects, there are provided pharmaceutical compositions comprising one or more of the above compounds and an excipient. In other aspects there are provided methods of treating and/or preventing a disease or a disorder in patients in need thereof, comprising administering to such patients one or more of the above compounds in an amount sufficient to treat and/or prevent the disease or disorder.

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

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

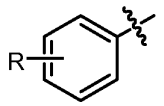
Disclosed herein are new compounds and compositions with antioxidant and/or anti-inflammatory properties, methods for their manufacture, and methods for their use, including for the treatment and/or prevention of disease.

I. 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" 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)−.

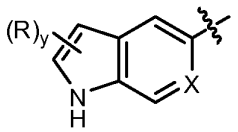
In the context of chemical formulas, the symbol "–" means a single bond, "=" means a double bond; and "≡" means triple bond. The symbol "----" represents an optional bond, which if present is either single or double. The symbol "----" represents a single bond or a double bond. Thus, for example, the structure  includes the structures  ,  ,  ,  and  . As will be understood by a person of skill in the art, 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 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:



,

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



,

then R may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (*e.g.*, the hydrogen attached to the nitrogen in the formula above), implied hydrogens (*e.g.*, a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (*e.g.,* a hydrogen attached to group X, when X equals −CH−), so long as a stable structure is formed. In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter "y" immediately following the group "R" enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

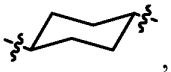
For the groups and classes below, the following parenthetical subscripts further define the group/class as follows: "(Cn)" defines the exact number (n) of carbon atoms in the group/class. "(C≤n)" defines the maximum number (n) of carbon atoms that can be in the group/class, with the minimum number as small as possible for the group in question, *e.g.*, it is understood that the minimum number of carbon atoms in the group "alkenyl$_{(C\leq 8)}$" or the class "alkene$_{(C\leq 8)}$" is two. For example, "alkoxy$_{(C\leq 10)}$" 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). (Cn-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)).

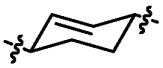
The term "saturated" as used herein means the compound or group so modified has no carbon-carbon double and no carbon-carbon triple bonds, except as noted below. The term does not preclude carbon-heteroatom multiple bonds, for example a carbon oxygen double bond or a carbon nitrogen double bond. Moreover, it does not preclude a carbon-carbon double bond that may occur as part of keto-enol 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 (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 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 $-S(O)_2NH_2$.

The term "alkyl" when used without the "substituted" modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, 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 $-CH_3$ (Me), $-CH_2CH_3$ (Et), $-CH_2CH_2CH_3$ (*n*-Pr), $-CH(CH_3)_2$ (*iso*-Pr), $-CH(CH_2)_2$ (cyclopropyl), $-CH_2CH_2CH_2CH_3$ (*n*-Bu), $-CH(CH_3)CH_2CH_3$ (*sec*-butyl), $-CH_2CH(CH_3)_2$ (*iso*-butyl), $-C(CH_3)_3$ (*tert*-butyl), $-CH_2C(CH_3)_3$ (*neo*-pentyl), 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, $-CH_2-$ (methylene), $-CH_2CH_2-$, $-CH_2C(CH_3)_2CH_2-$, $-CH_2CH_2CH_2-$, and  , are non-limiting examples of alkanediyl groups. The term "alkylidene" when used without the "substituted" modifier refers to the divalent group =CRR′ in which R and R′ are independently hydrogen, 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: $=CH_2$, $=CH(CH_2CH_3)$, and $=C(CH_3)_2$. When any of these terms is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$. The following groups are non-limiting examples of substituted alkyl groups: $-CH_2OH$, $-CH_2Cl$, $-CF_3$, $-CH_2CN$, $-CH_2C(O)OH$, $-CH_2C(O)OCH_3$, $-CH_2C(O)NH_2$, $-CH_2C(O)CH_3$, $-CH_2OCH_3$, $-CH_2OC(O)CH_3$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$, and $-CH_2CH_2Cl$. The term "haloalkyl" is a subset of substituted alkyl, in which one or more hydrogen atoms has been substituted with a halo group and no other atoms aside from carbon, hydrogen and halogen are present. The group, $-CH_2Cl$ is a non-limiting examples of a haloalkyl. An "alkane" refers to the compound H−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, $-CH_2F$, $-CF_3$, and $-CH_2CF_3$ are non-limiting examples of fluoroalkyl groups. An "alkane" refers to the compound H−R, wherein R is alkyl.

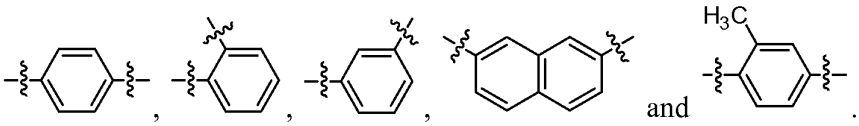
The term "alkenyl" when used without the "substituted" modifier refers to an monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: $-CH=CH_2$ (vinyl), $-CH=CHCH_3$, $-CH=CHCH_2CH_3$, $-CH_2CH=CH_2$ (allyl), $-CH_2CH=CHCH_3$, and $-CH=CH-C_6H_5$. 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, $-CH=CH-$,

−CH=C(CH$_3$)CH$_2$−, −CH=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 −OH, −F, −Cl, −Br, −I, −NH$_2$, −NO$_2$, −CO$_2$H, −CO$_2$CH$_3$, −CN, −SH, −OCH$_3$, −OCH$_2$CH$_3$, −C(O)CH$_3$, −N(CH$_3$)$_2$, −C(O)NH$_2$, −OC(O)CH$_3$, or −S(O)$_2$NH$_2$. The groups, −CH=CHF, −CH=CHCl and −CH=CHBr, are non-limiting examples of substituted alkenyl groups. An "alkene" refers to the compound H−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 carbon-carbon triple bond, and no atoms other than carbon and hydrogen. As used herein, the term alkynyl does not preclude the presence of one or more non-aromatic carbon-carbon double bonds. The groups, −C≡CH, −C≡CCH$_3$, and −CH$_2$C≡CCH$_3$, are non-limiting examples of alkynyl groups. When alkynyl is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by −OH, −F, −Cl, −Br, −I, −NH$_2$, −NO$_2$, −CO$_2$H, −CO$_2$CH$_3$, −CN, −SH, −OCH$_3$, −OCH$_2$CH$_3$, −C(O)CH$_3$, −N(CH$_3$)$_2$, −C(O)NH$_2$, −OC(O)CH$_3$, or −S(O)$_2$NH$_2$. An "alkyne" refers to the compound H−R, wherein R is alkynyl.

The term "aryl" when used without the "substituted" modifier refers to a monovalent unsaturated aromatic group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a one or more six-membered aromatic ring structure, wherein the ring atoms are all carbon, and wherein the group consists of no atoms other than carbon and hydrogen. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl group (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, −C$_6$H$_4$CH$_2$CH$_3$ (ethylphenyl), naphthyl, and the monovalent group derived from biphenyl. The term "arenediyl" when used without the "substituted" modifier refers to a divalent aromatic group, with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. As used herein, the term does not preclude the presence of

one or more alkyl group (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. If more than one ring is present, the rings may be fused or unfused. Non-limiting examples of arenediyl groups include:



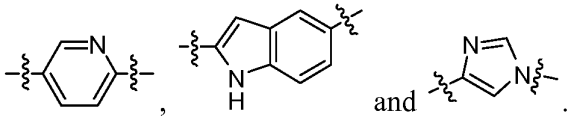
and .

When these terms are used with the "substituted" modifier one or more hydrogen atom has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$. An "arene" refers to the compound H−R, wherein R is aryl.

The term "aralkyl" when used without the "substituted" modifier refers to the monovalent group −alkanediyl−aryl, in which the terms alkanediyl and aryl are each used in a manner consistent with the definitions provided above. Non-limiting examples 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 −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 $-S(O)_2NH_2$. 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

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 $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$.

The term "heterocycloalkyl" when used without the "substituted" modifier refers to a monovalent non-aromatic group with a carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of one or more non-aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heterocycloalkyl group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. 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, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, and pyranyl. When the term "heterocycloalkyl" used with the "substituted" modifier one or more hydrogen atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$.

The term "acyl" when used without the "substituted" modifier refers to the group $-C(O)R$, in which R is a hydrogen, alkyl, aryl, aralkyl or heteroaryl, as those

terms are defined above. The groups, −CHO, −C(O)CH_3 (acetyl, Ac), −C(O)CH_2CH_3, −C(O)$CH_2CH_2CH_3$, −C(O)$CH(CH_3)_2$, −C(O)$CH(CH_2)_2$, −C(O)C_6H_5, −C(O)$C_6H_4CH_3$, −C(O)$CH_2C_6H_5$, −C(O)(imidazolyl) are non-limiting examples of acyl groups. A "thioacyl" is defined in an analogous manner, except that the oxygen atom of the group −C(O)R has been replaced with a sulfur atom, −C(S)R. 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−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 $-S(O)_2NH_2$. The groups, −C(O)CH_2CF_3, $-CO_2H$ (carboxyl), $-CO_2CH_3$ (methylcarboxyl), $-CO_2CH_2CH_3$, $-C(O)NH_2$ (carbamoyl), and $-CON(CH_3)_2$, are non-limiting examples of substituted acyl groups.

The term "alkoxy" when used without the "substituted" modifier refers to the group −OR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkoxy groups include: $-OCH_3$ (methoxy), $-OCH_2CH_3$ (ethoxy), $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$ (isopropoxy), $-OCH(CH_2)_2$, −O−cyclopentyl, and −O−cyclohexyl. The terms "alkenyloxy", "alkynyloxy", "aryloxy", "aralkoxy", "heteroaryloxy", and "acyloxy", when used without the "substituted" modifier, refers to groups, defined as −OR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, and acyl, respectively. The term "alkoxydiyl" refers to the divalent group −O−alkanediyl−, −O−alkanediyl−O−, or −alkanediyl−O−alkanediyl−. The term "alkylthio" and "acylthio" when used without the "substituted" modifier refers to the group −SR, in which R is an alkyl and acyl, respectively. When any of these terms is used with the "substituted" modifier one or more hydrogen atom has been independently replaced by −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$. 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 −NHR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkylamino groups include: $-NHCH_3$ and $-NHCH_2CH_3$. The term "dialkylamino" when used without the "substituted" modifier refers to the group −NRR′, in which R and R′ can be the same or different alkyl groups, or R and R′ can be taken together to represent an alkanediyl. Non-limiting examples of dialkylamino

groups include: $-N(CH_3)_2$, $-N(CH_3)(CH_2CH_3)$, 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 $-NHC_6H_5$. The term "amido" (acylamino), when used without the "substituted" modifier, refers to the group −NHR, in which R is acyl, as that term is defined above. A non-limiting example of an amido group is $-NHC(O)CH_3$. The term "alkylimino" when used without the "substituted" modifier refers to the divalent group =NR, in which R is an alkyl, as that term is defined above. The term "alkylaminodiyl" refers to the divalent group −NH−alkanediyl−, −NH−alkanediyl−NH−, or −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, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$. 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 $-S(O)_2R$ 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, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, −CN, −SH, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-OC(O)CH_3$, or $-S(O)_2NH_2$.

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 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 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 compound has less than one (*e.g.*, hemihydrate), one (*e.g.*, monohydrate), or more than one (*e.g.*, dihydrate) water molecules associated with each compound molecule, such as in solid forms of the compound.

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

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

As used herein, the term "patient" or "subject" refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

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

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

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

not yet experience or display any or all of the pathology or symptomatology of the disease.

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

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 which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. "Enantiomers" are stereoisomers of a given compound that are mirror images of each other, like left and right hands. "Diastereomers" are stereoisomers of a given compound that are not enantiomers. Chiral molecules contain a chiral center, also referred to as a stereocenter or stereogenic center, which is any point, though not necessarily an atom, in a molecule bearing groups such that an interchanging of any two groups leads to a stereoisomer. In organic compounds, the chiral center is typically a carbon, phosphorus or sulfur atom, though it is also possible for other atoms to be stereocenters in organic and inorganic compounds. A molecule can have multiple stereocenters, giving it many stereoisomers. In compounds whose stereoisomerism is due to tetrahedral stereogenic centers (*e.g.*, tetrahedral carbon), the total number of hypothetically possible stereoisomers will not exceed 2n, 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 diasteromers can be resolved or separated using techniques known in the art. It is contemplated that that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its *R* form, *S* form, or as a mixture of the *R* and *S* forms, including racemic and non-racemic mixtures. As used herein, the phrase "substantially free from other stereoisomers" means that the composition contains $\leq$ 15%, more preferably $\leq$ 10%, even more preferably $\leq$ 5%, or most preferably $\leq$ 1% of another stereoisomer(s).

"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; IFNγ or IFN-γ, interferon-γ; TNFα or TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; 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 ($-C(O)OC(CH_3)_3$, Boc), benzyloxycarbonyl, *p*-methoxy-benzyloxycarbonyl, 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 ($-C(O)OC(CH_3)_3$, Boc), and the like. Suitable peptide residues include peptide residues comprising two to five amino

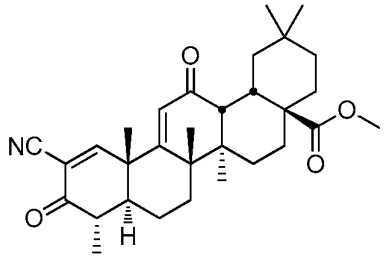
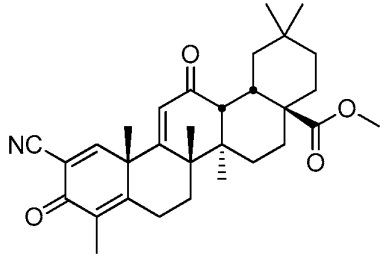
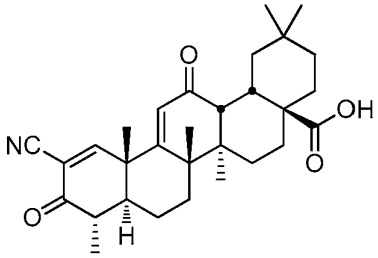
acid residues. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric 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 ($-C(O)OC(CH_3)_3$), 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).

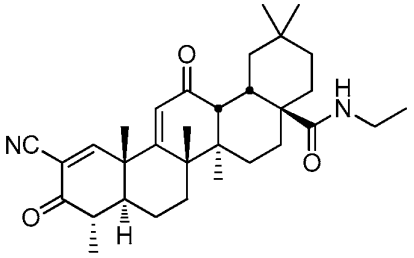
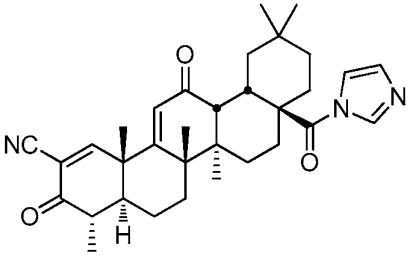
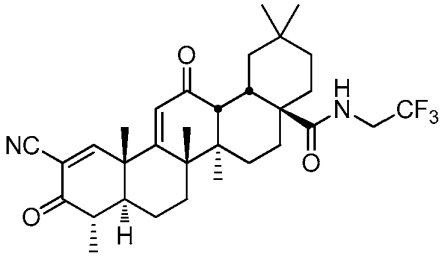
Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (*e.g.*, higher oral bioavailability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

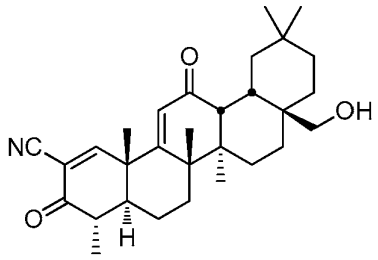
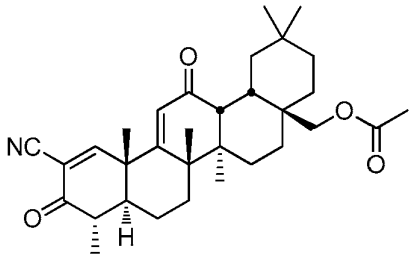
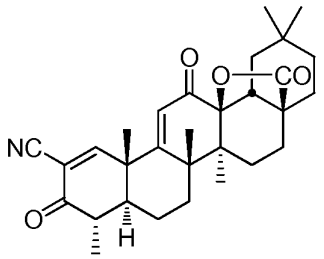
III. Biological Activity

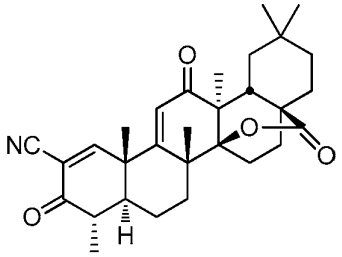
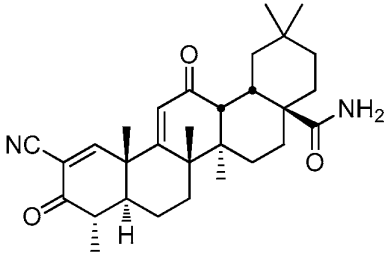
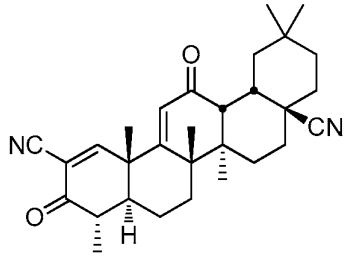
Assay results for the suppression of IFNγ-induced NO production are shown for several of the compounds of the present invention in Table 1 below. In the right-hand column of this table under the RAW264.7 heading, the results are compared to those of bardoxolone methyl (RTA 402, CDDO-Me). Available NQO1-ARE Luciferase reporter assay results are shown in the last column. Details regarding both assays are provided in the Examples section below.

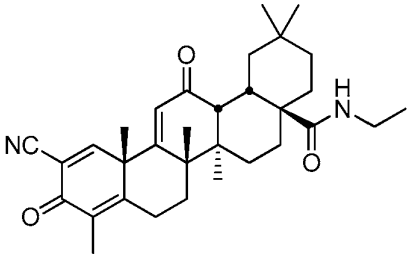
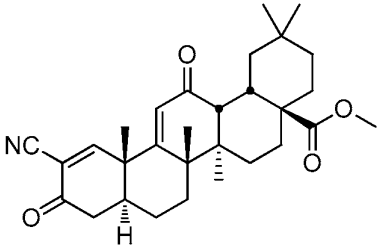
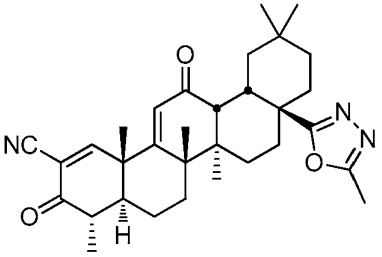
Table 1. Suppression of IFNγ-Induced NO Production.

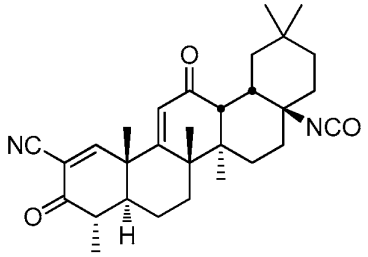
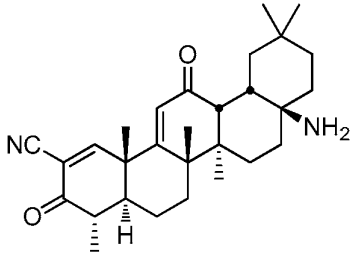
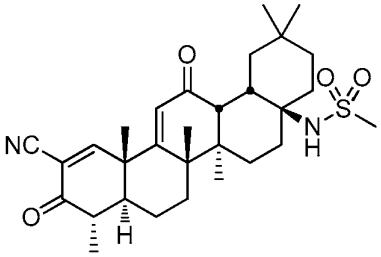
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63435		491.66	1.0	0.4	7.2
TX63448		489.65	75	44	
TX63520		477.63	10.1	6.7	5.3

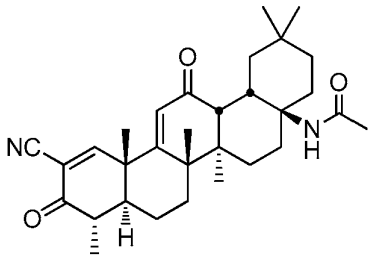
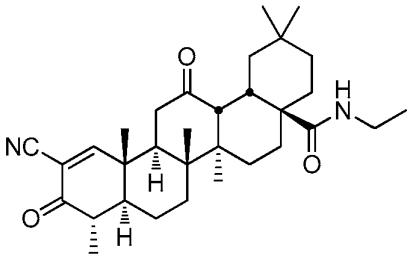
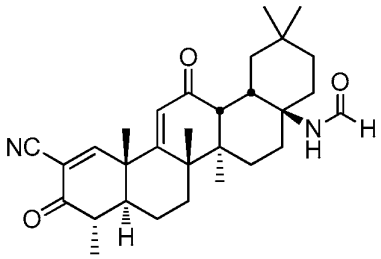
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63521		504.70	1.1	0.6	
TX63522		527.70	0.4	0.3	4.1
TX63523		558.67	1.0	0.6	5.6

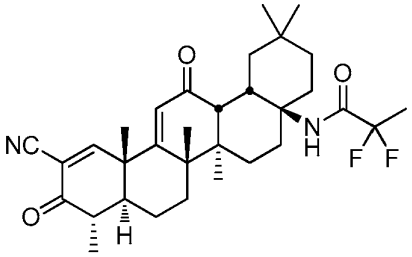
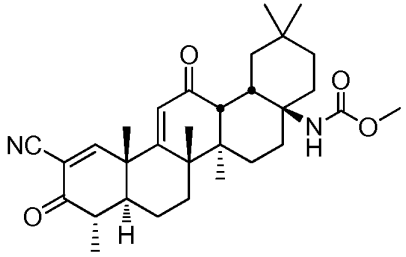
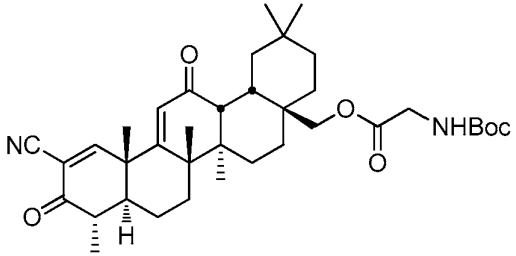
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63545		463.65	0.7	0.3	7.2
TX63546		505.69	1.0	0.6	
TX63555		475.62	1.4	0.5	6.1

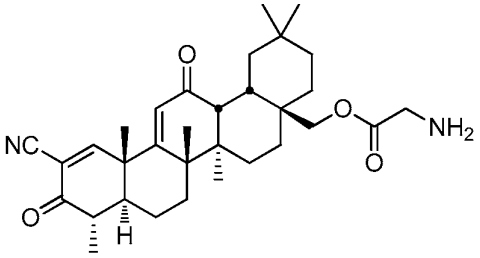
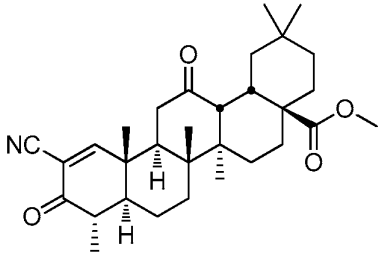
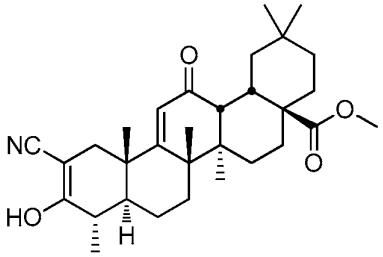
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63556		475.62	69.0	25.6	
TX63557		476.65	2.2	1.0	
TX63558		458.63	0.6	0.3	

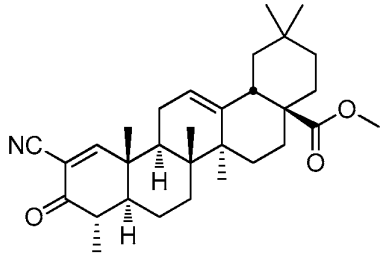
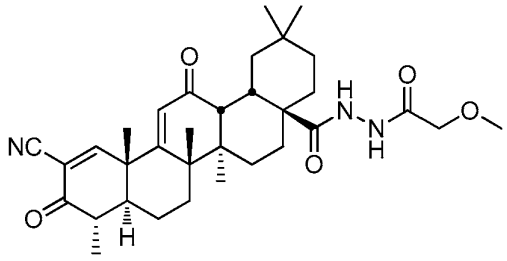
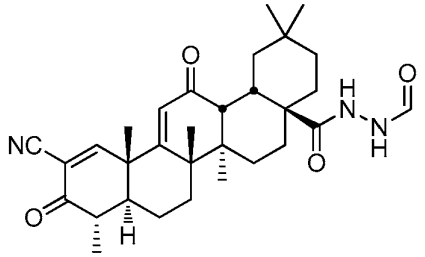
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63597		502.69	>25	>12	
TX63614		477.63	11.7	5.9	
TX63616		515.69	0.7	0.5	4.4

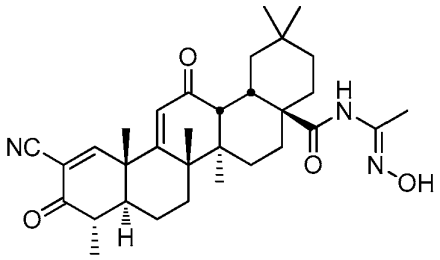
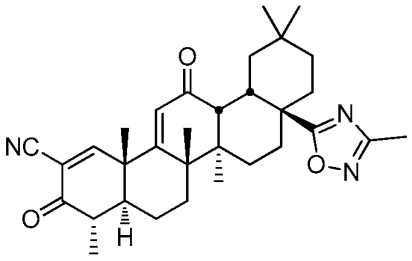
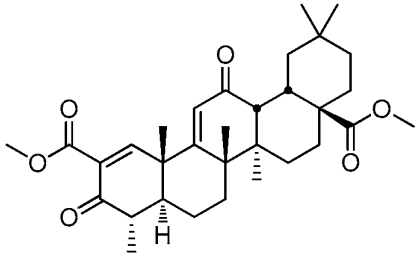
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63618		474.63	8.2	5.9	
TX63620		448.64	1.2	0.9	
TX63621		526.73	0.8	0.6	

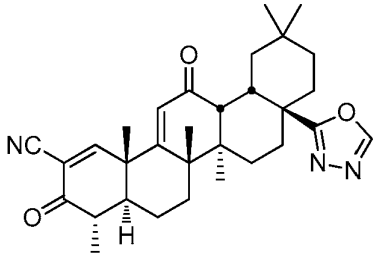
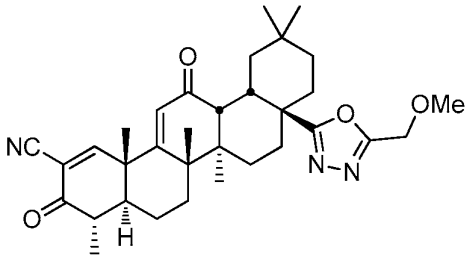
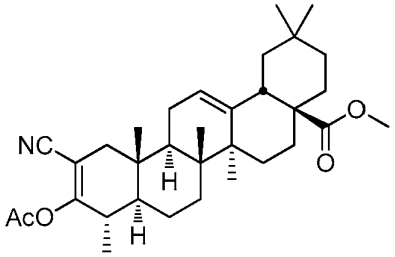
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63622		490.68	3.8	2.3	
TX63680		506.72	7.0	3.6	
TX63681		476.65	1.6	1.1	

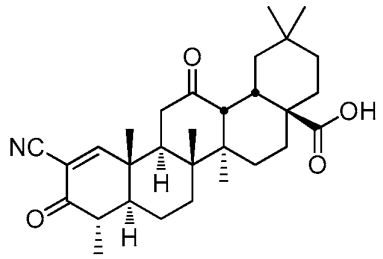
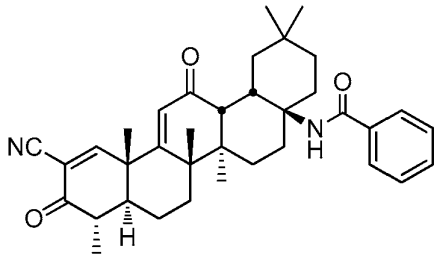
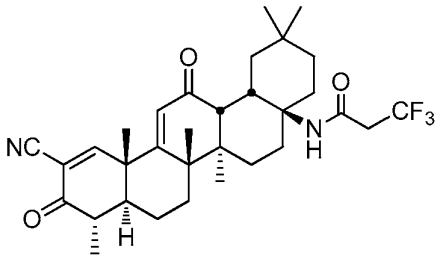
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63682		540.68	1.1	0.65	5.7
TX63693		506.68	1.4	0.8	
TX63716		620.82	3.2	2.0	

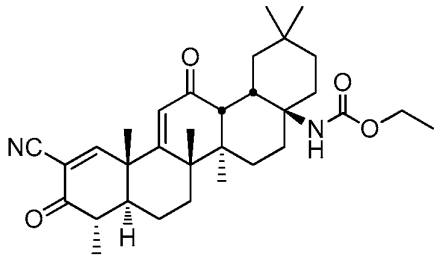
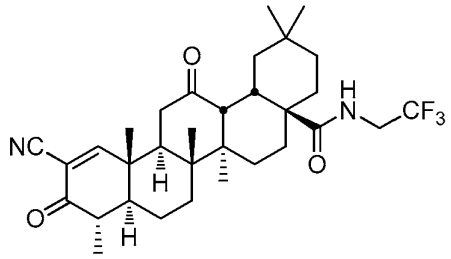
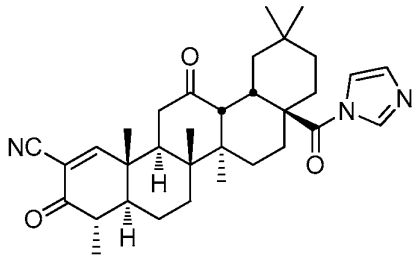
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63717		520.70	0.6	0.4	
TX63749		493.68	3.0	2.1	2.3
TX63778		493.68	50	39	

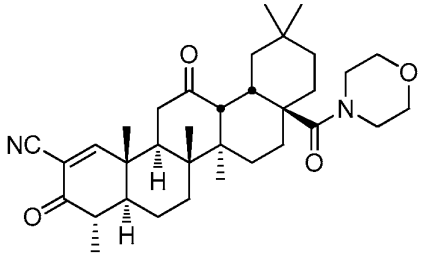
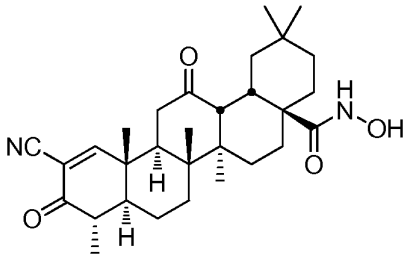
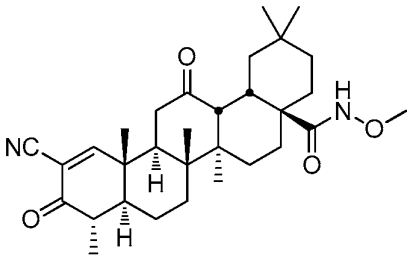
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63779		477.68	44	34	
TX63784		563.73	7.5	6.2	
TX63785		519.67	20.0	16.4	

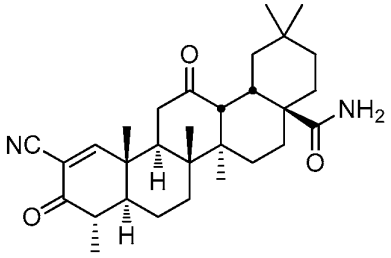
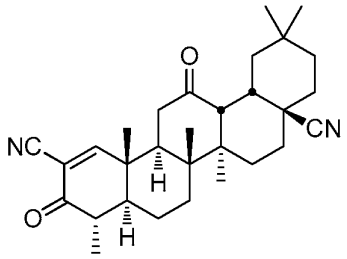
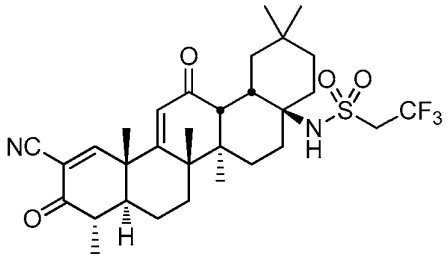
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63786		533.70	2.2	1.8	
TX63787		515.69	0.8	0.4	
TX63788		524.69	33.5	32	

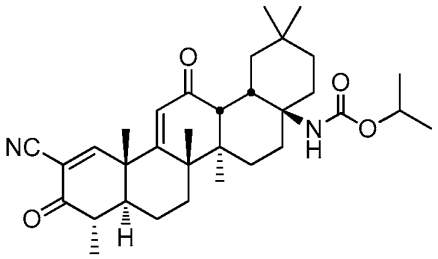
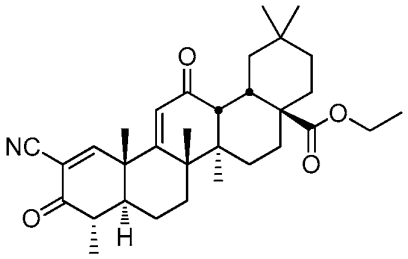
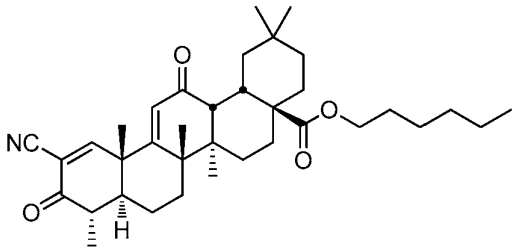
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63789		501.66	0.6	0.3	
TX63790		545.71	1.1	0.6	
TX63795		521.73	>200	NA	

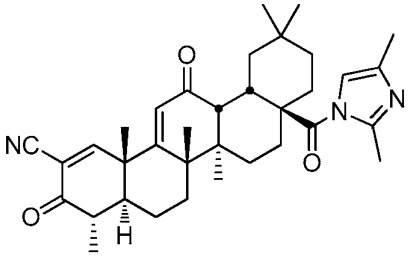
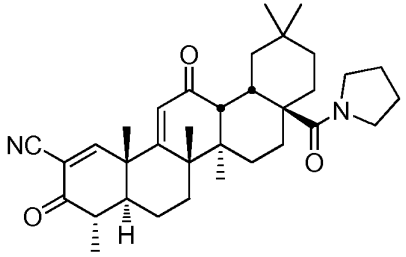
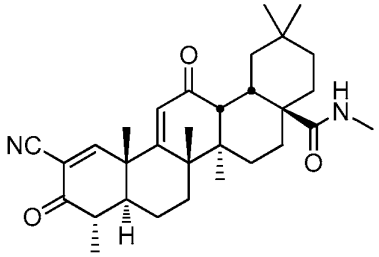
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63797		479.65	21	17	
TX63798		552.75	1.5	1.2	
TX63799		558.67	1.8	1.6	

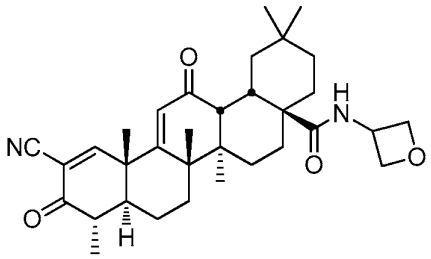
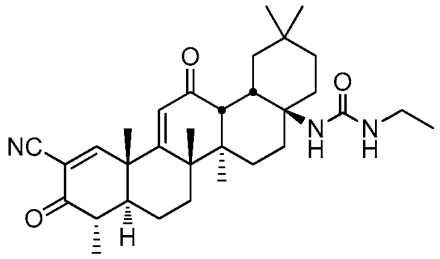
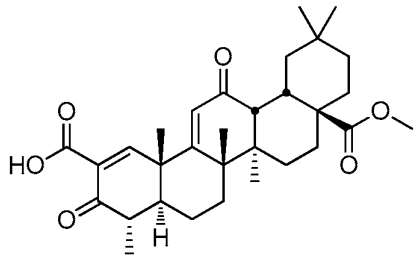
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63800		520.70	0.9	0.8	
TX63807		560.69	5.8	2.6	
TX63811		529.71	0.3	0.2	

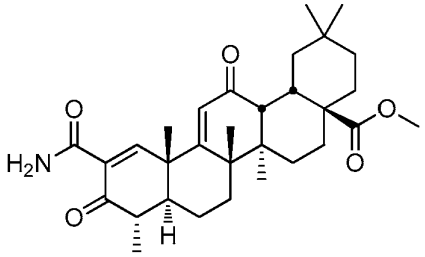
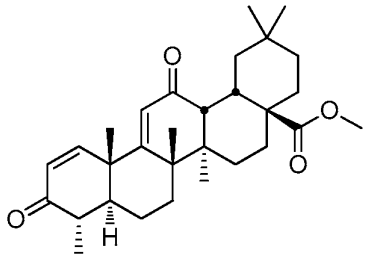
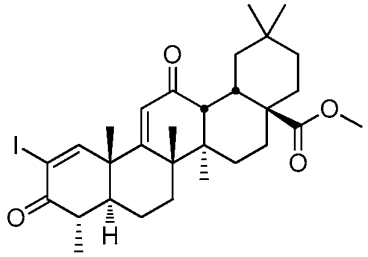
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63812		548.76	10.1	4.4	
TX63814		494.67	19.0	8.3	
TX63815		508.69	9.6	4.2	

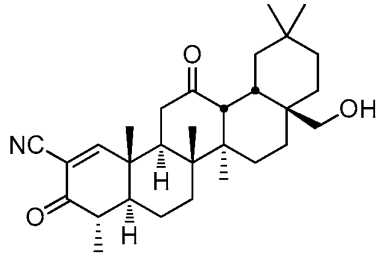
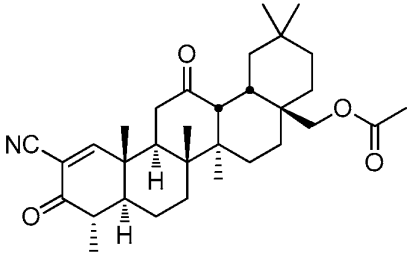
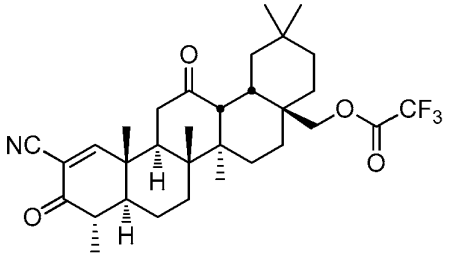
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63816		478.67	10.2	4.5	
TX63817		460.65	2.6	1.1	
TX63818		594.73	0.8	0.6	

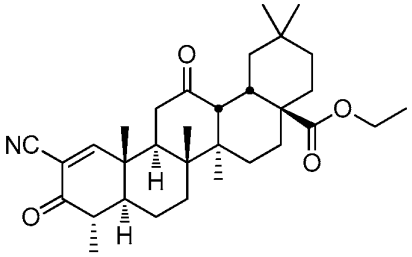
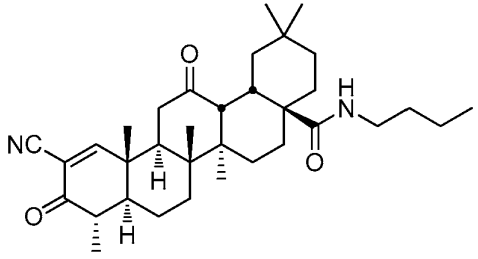
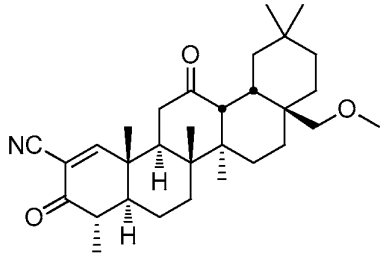
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63819		534.73	2.7	2.2	
TX63820		505.69	1.5	1.2	
TX63821		561.79	53	41	

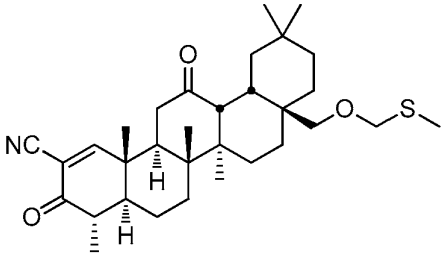
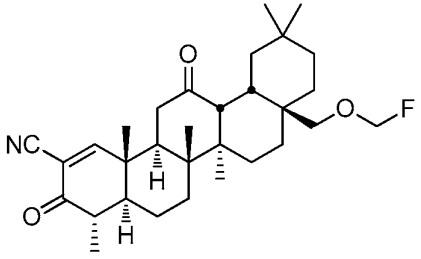
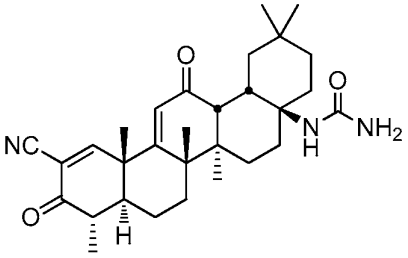
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63822		555.75	0.7	0.6	
TX63823		530.74	0.8	0.6	
TX63824		490.68	1.0	0.5	

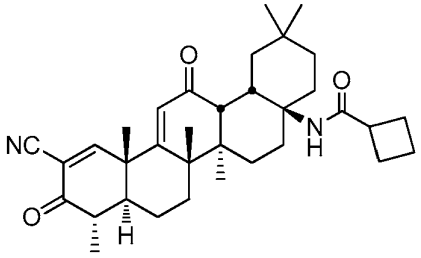
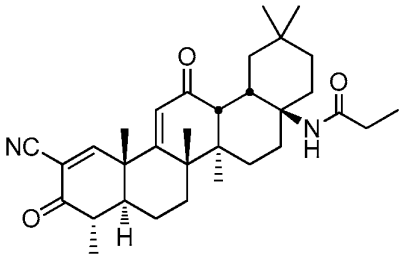
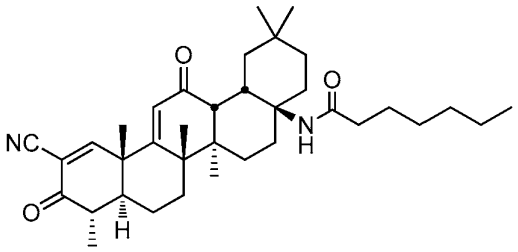
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63825		532.71	2.0	1.5	
TX63826		519.72	4.4	3.5	
TX63830		510.66	4.6	3.6	

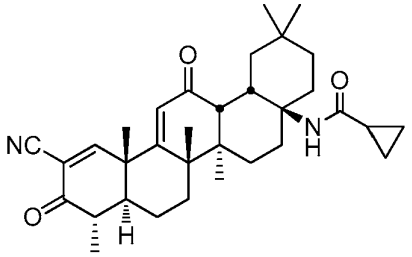
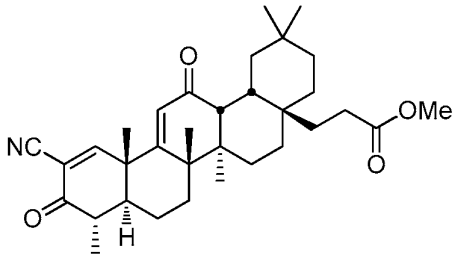
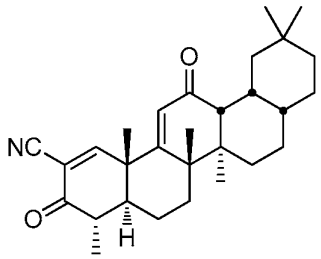
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63831		509.68	21	16.4	
TX63832		466.65	149	89	
TX63833		592.55	88	63	

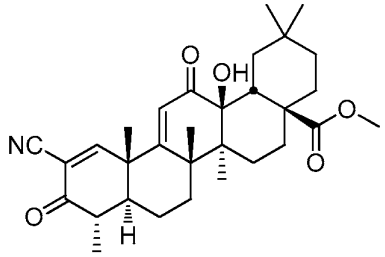
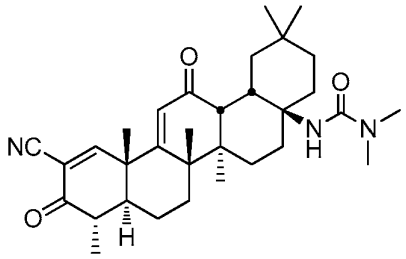
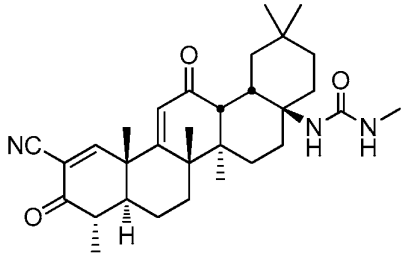
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63839		465.67	4.0	2.9	
TX63840		507.70	2.9	2.1	
TX63841		561.68	4.5	3.2	

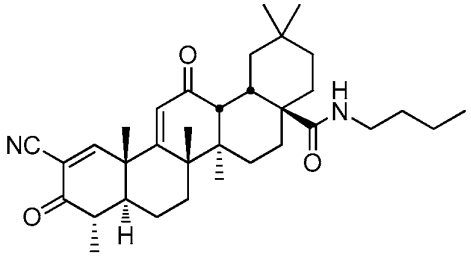
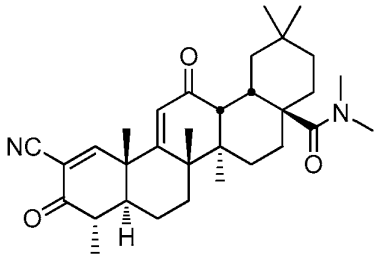
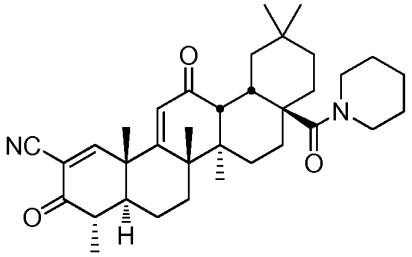
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63842		507.70	6.1	4.3	
TX63843		534.77	10.9	7.8	
TX63858		479.69	7.2	3.7	

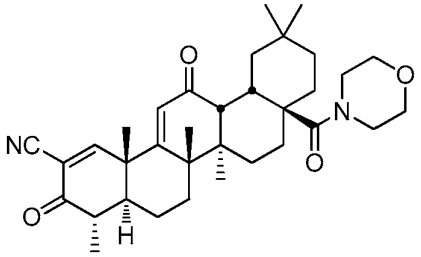
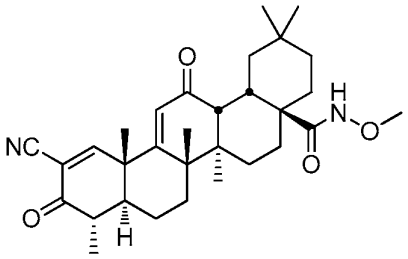
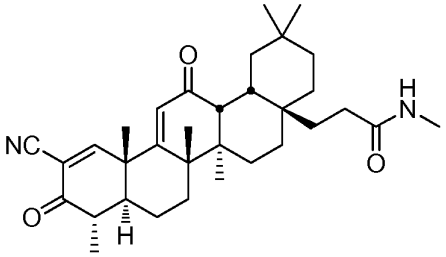
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63859		525.79	14.6	7.4	
TX63860		497.68	4.1	2.1	
TX63862		491.66	28	22.7	

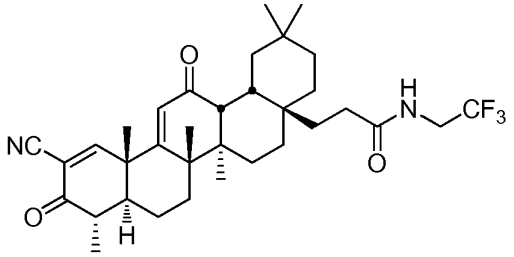
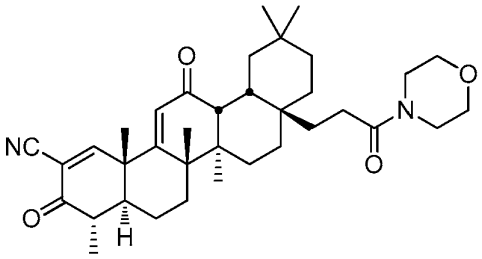
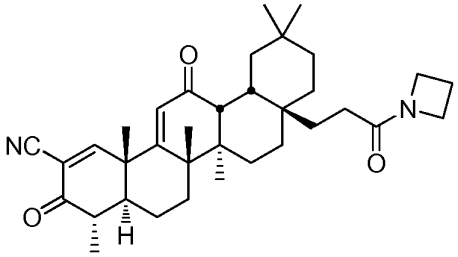
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63863		530.74	1.8	1.5	
TX63864		504.70	1.9	1.5	
TX63865		560.81	9.4	7.6	

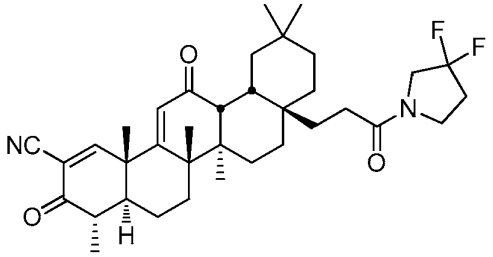
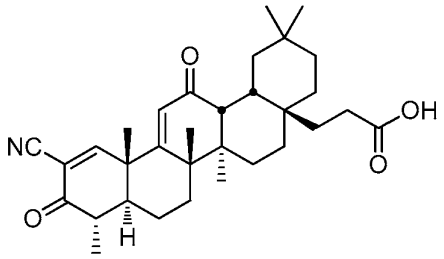
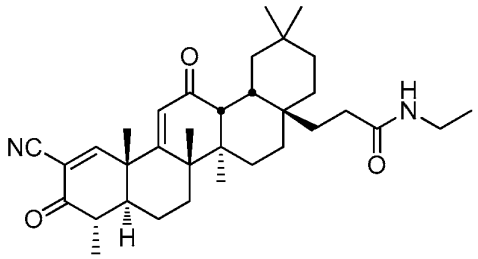
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63866		516.71	1.4	1.2	
TX63867		519.71	1.3	0.7	
TX63869		433.63	3.8	2.9	

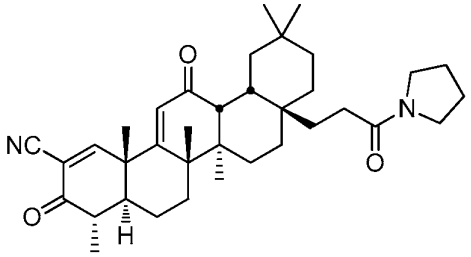
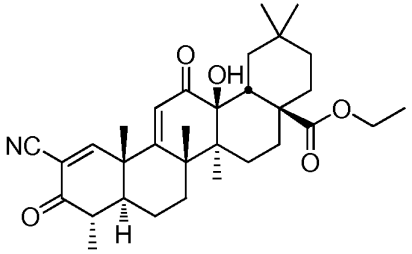
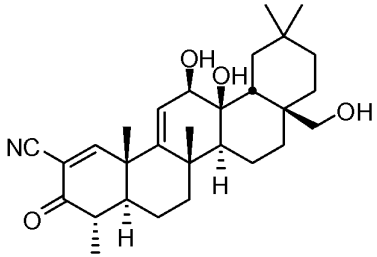
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63870		507.66	1.1	0.7	
TX63875		519.72	1.3	1.0	
TX63876		505.69	7.3	5.8	

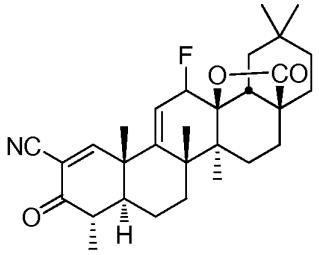
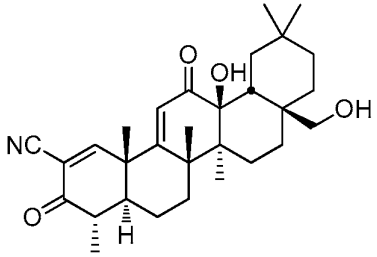
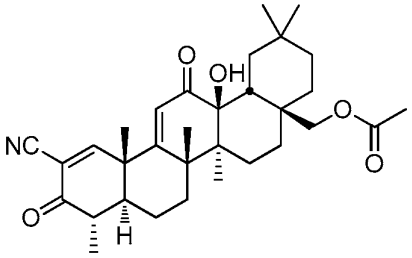
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63877		532.76	1.3	1.1	
TX63878		504.70	1.4	0.9	
TX63880		544.77	1.6	1.2	

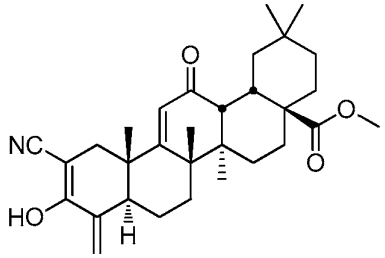
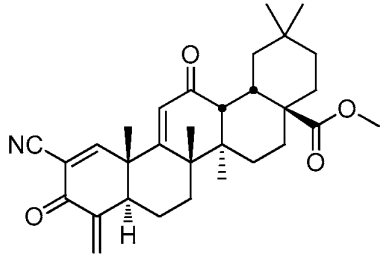
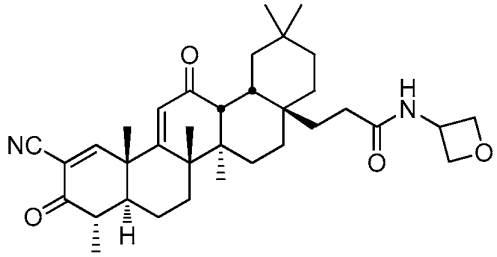
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63881		546.74	0.9	0.7	
TX63882		506.68	1.6	1.2	
TX63886		518.73	0.3	0.2	

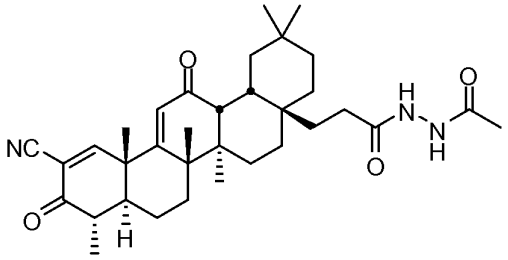
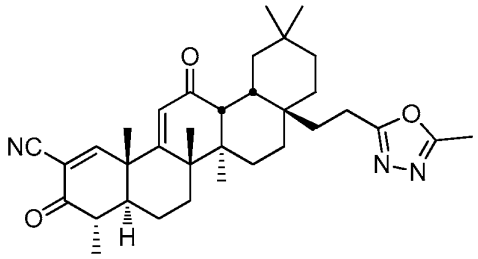
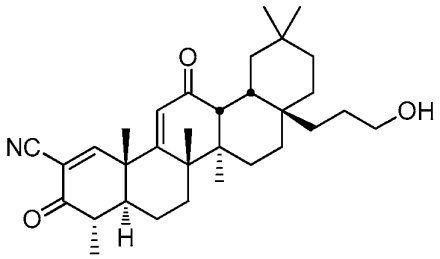
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63887		586.73	0.8	0.6	
TX63888		574.79	0.3	0.3	
TX63889		544.77	0.4	0.3	

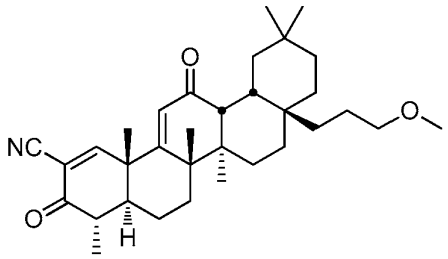
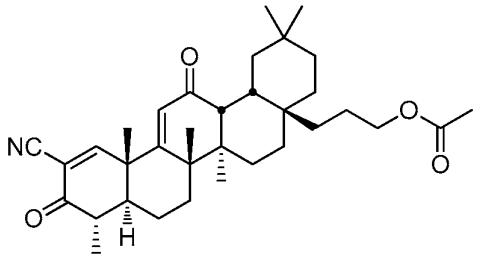
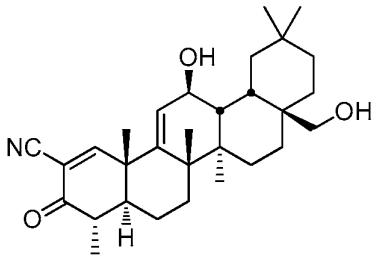
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63890		594.77	0.8	0.6	
TX63891		505.69	1.3	1.1	
TX63892		532.76	0.3	0.2	

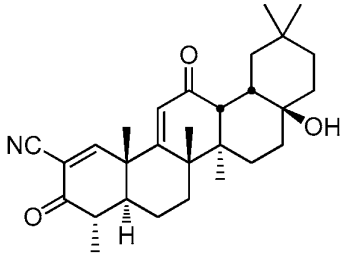
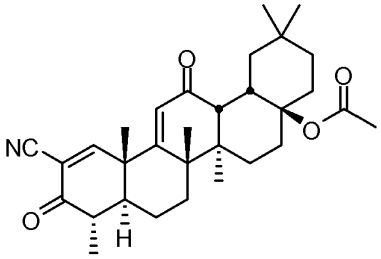
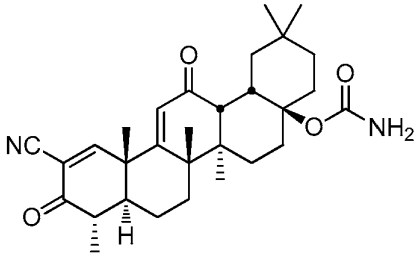
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63893		558.79	0.5	0.4	
TX63901		521.69	1.3	0.8	
TX63904		481.67	10.4	6.3	

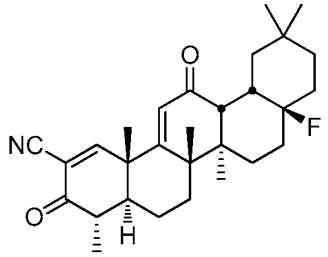
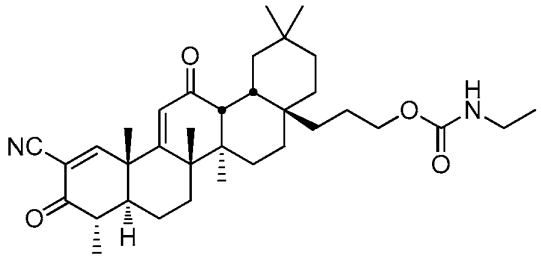
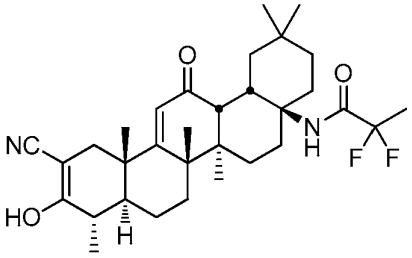
Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63907		479.63	1.6	1.0	
TX63908		479.65	0.6	0.4	
TX63909		521.69	1.4	0.8	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63910		491.66	304	230	
TX63911		489.65	10.0	7.6	
TX63914		560.77	0.4	0.3	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63915		561.75	4.0	3.1	
TX63916		543.74	0.4	0.3	
TX63918		491.70	0.5	0.5	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63919		505.73	1.4	1.2	
TX63920		533.74	0.9	0.8	
TX63923		465.67	2.5	1.8	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63925		449.62	0.4	0.3	
TX63928		491.66	0.6	0.4	
TX63929		492.65	0.5	0.3	

Compound No.	Molecular Structure	MW	RAW264.7		NQO1-ARE assay
			NO IC_{50} (nM)	Relative NO IC_{50}	Fold induction at 62.5 nM
TX63936		451.62	1.1	0.7	
TX63982		562.78	3.5	1.4	
TX63984		542.70	48	18	

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, COPD, and idiopathic pulmonary fibrosis, 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, 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 has also been linked to major mental illness. Therefore, downregulating inflammatory cytokines and inhibiting excessive activation of microglia could be beneficial in patients with schizophrenia, major depression, bipolar disorder, autism-spectrum disorders, and other neuropsychiatric disorders.

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

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

In some embodiments, the compounds disclosed herein may be used in the treatment and prevention of diseases such as cancer, inflammation, Alzheimer's disease, Parkinson's disease, multiple sclerosis, autism, amyotrophic lateral sclerosis, Huntington's disease, autoimmune diseases such as rheumatoid arthritis, lupus, Crohn's disease and psoriasis, inflammatory bowel disease, all other diseases whose pathogenesis is believed to involve excessive production of either nitric oxide or

prostaglandins, and pathologies involving oxidative stress alone or oxidative stress exacerbated by inflammation.

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

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

To administer the therapeutic compound by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the therapeutic compound may be administered to a patient in an appropriate carrier, for example, 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).

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

Pharmaceutical compositions 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, 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 (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 ± 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 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 includes both agents, or with two distinct compositions or formulations, administered at the same time, wherein one composition includes a compound of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

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

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 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

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% CO_2. 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 IFNγ (R&D Systems) for 24 hours. Nitric Oxide concentration in media was determined using the Griess reagent system (Promega). Cell viability was determined using WST-1 reagent (Roche). IC_{50} values were determined based on the suppression of IFNγ 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 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:

5′- CAGTCACAGTGACTCAGCAGAATCTG-3′ (SEQ ID NO:1)

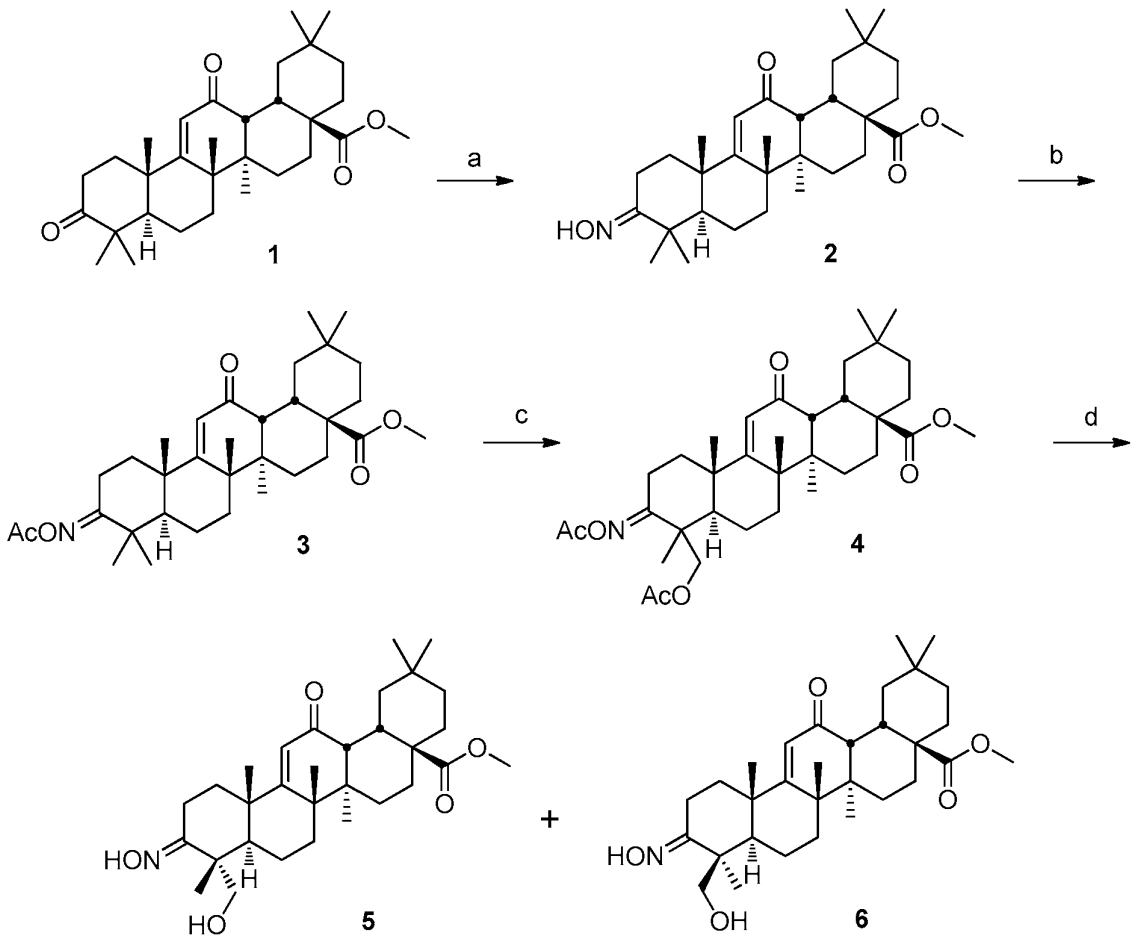
encompassing the human NQO1-ARE into the pLuc-MCS vector using HindIII/XhoI cloning sites (GenScript Corp., Piscataway, NJ). The assay is performed in HuH7 cells maintained in DMEM (Invitrogen) supplemented with 10% FBS and 100U/ml (each) of penicillin and streptomycin. For the assay, cells are plated in 96-well plates 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 concentrations ranging from 0 to 1 μM) 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 *et al.*, 1995, which is incorporated herein by reference.

5

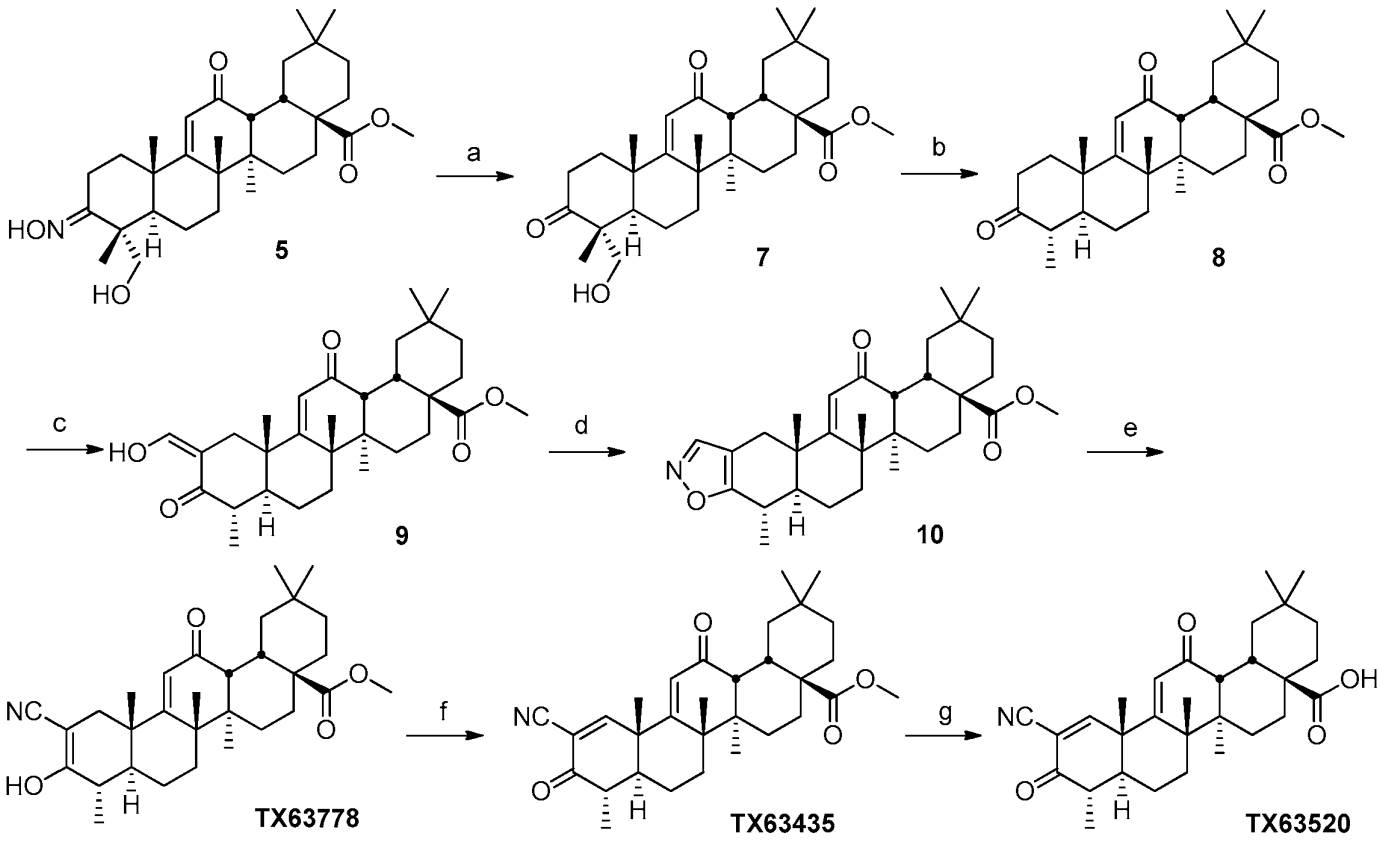
Synthetic Schemes, Reagents and Yields

Scheme 1



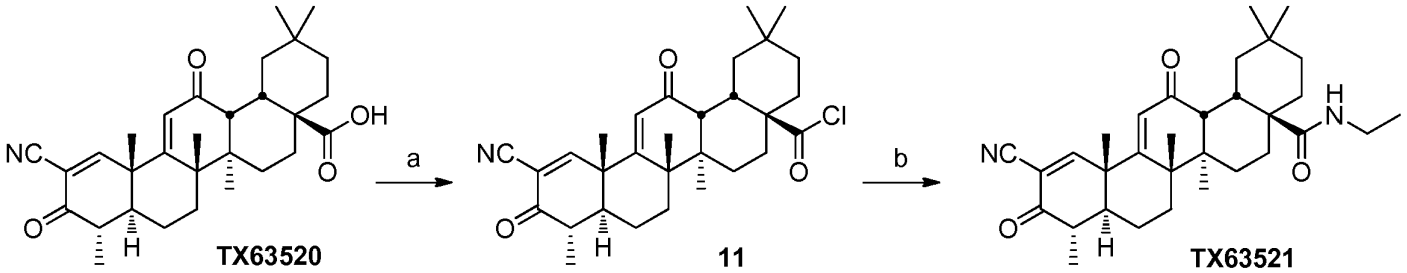
Reagents and conditions: a) NH_2OH-HCl, NaOAc, CH_2Cl_2, MeOH, 70 °C, 1.5 h; b) AcOH, Ac_2O, rt, 2 h; c) $PhI(OAc)_2$, $Pd(OAc)_2$, 60 °C, 24 h, 48% from **1**; d) K_2CO_3, MeOH, 0 °C-rt, 1 h, 75% for **5**, 11% for **6**.

Scheme 2



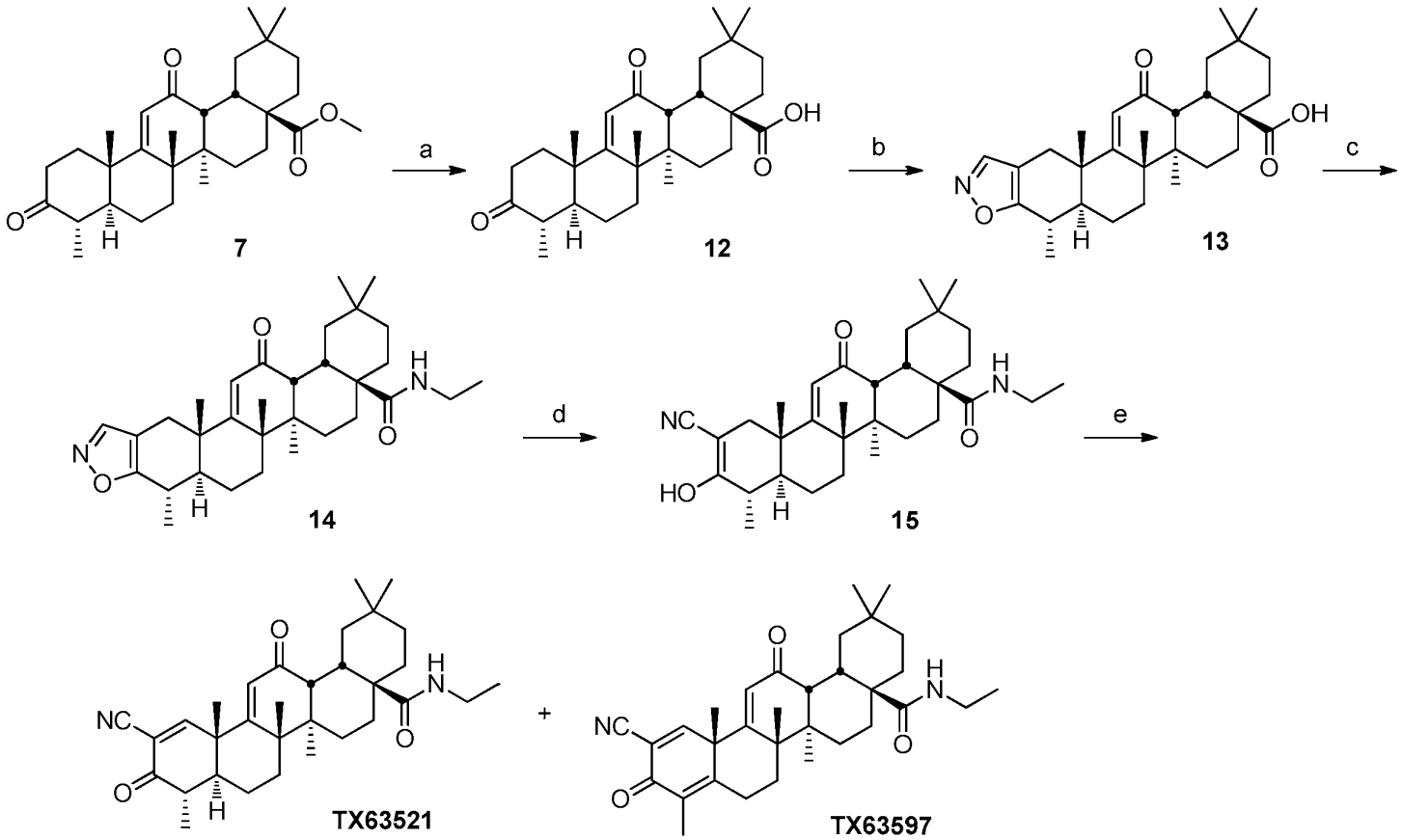
Reagents and conditions: a) $NaHSO_3$, aq. EtOH, reflux, 3 h, 85%; b) xylene, reflux, 28 h, 85%; c) HCO_2Et, NaOMe, 0 °C-rt, 2.5 h; d) NH_2OH-HCl, aq. EtOH, 55 °C, 3 h, 76% from **7**; e) NaOMe, MeOH, 55 °C, 2 h; f) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Py, 55 °C, 3.5 h, 85% from **9**; g) LiI, DMF, 150 °C, 4 h, 64%.

Scheme 3



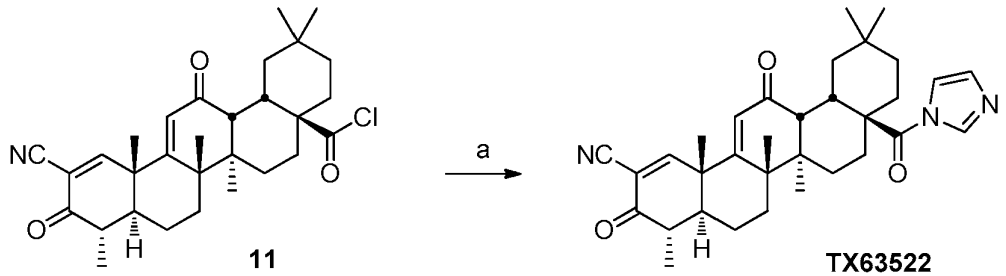
Reagents and conditions: a) oxalyl chloride, DMF (cat.), CH_2Cl_2, 0 °C-rt, 2 h; b) $EtNH_2$, CH_2Cl_2, THF, 0 °C, 30 min, 100%.

Scheme 4. Alternative synthetic route to TX63521



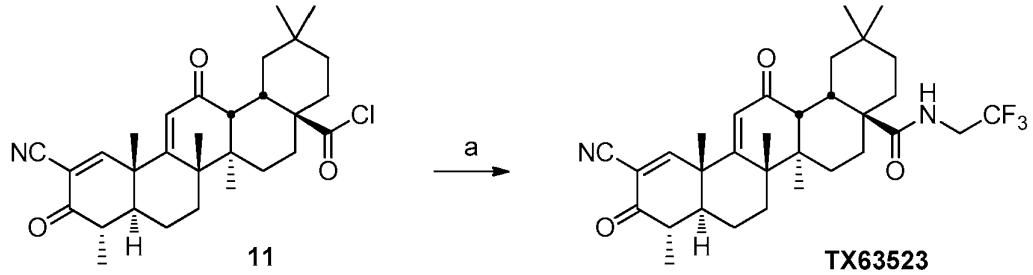
Reagents and conditions: a) LiI, DMF, 150 °C, 5-8 h, 93%; b) (i) HCOOEt, NaOMe, MeOH, 0 °C to rt, 1 h; (ii) NH_2OH-HCl, 55 °C, 3 h, 80%; c) (i) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 2 h; (ii) $EtNH_2$, CH_2Cl_2, THF, 0 °C, 40 min, 86%; d) NaOMe, MeOH, 55 °C, 2 h, 92%; e) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Py, 55 °C, 3 h, 82%.

Scheme 5



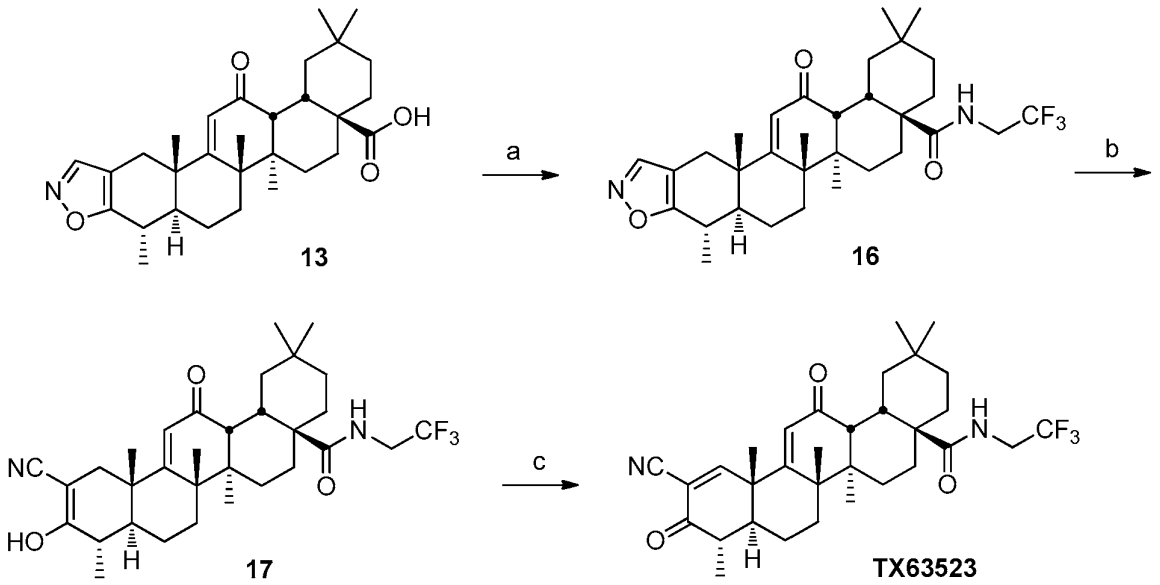
Reagents and conditions: a) imidazole, benzene, 10 °C, 70 min, 77%.

Scheme 6



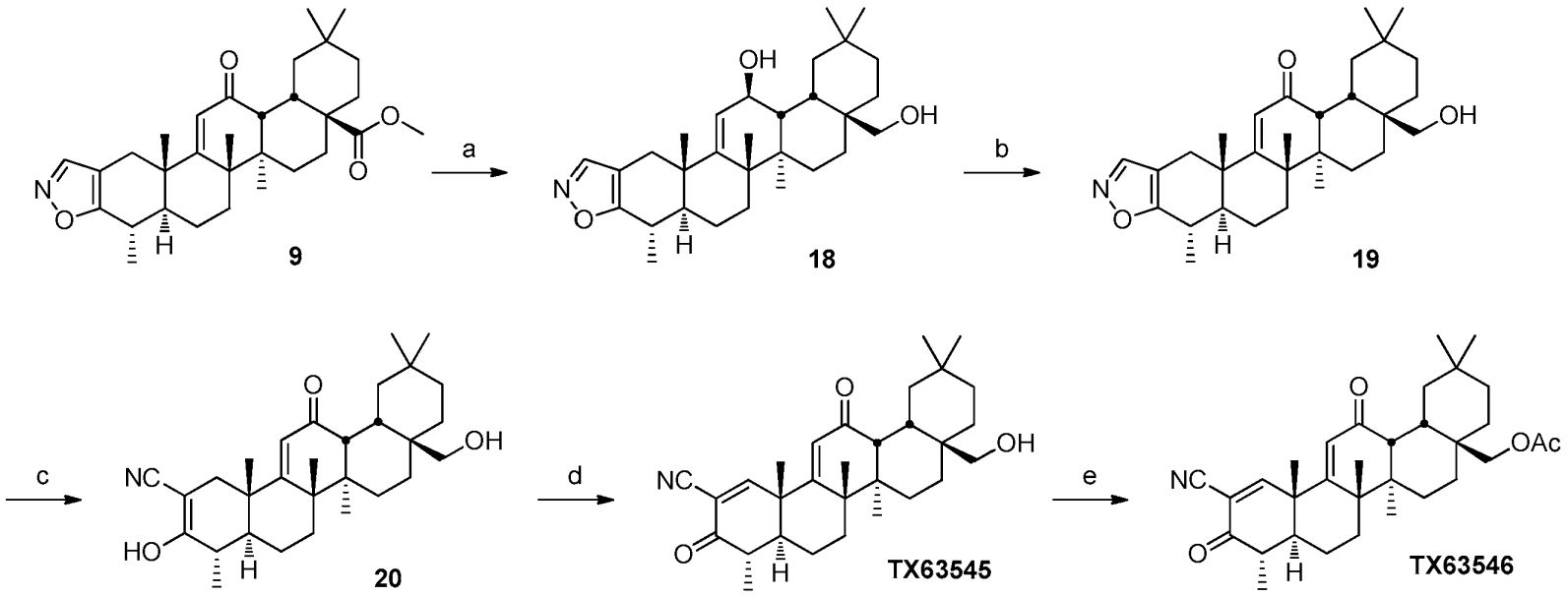
Reagents and conditions: a) $CF_3CH_2NH_2$, CH_2Cl_2, rt, 1 h, 82%.

Scheme 7. Alternative synthetic route to TX63523



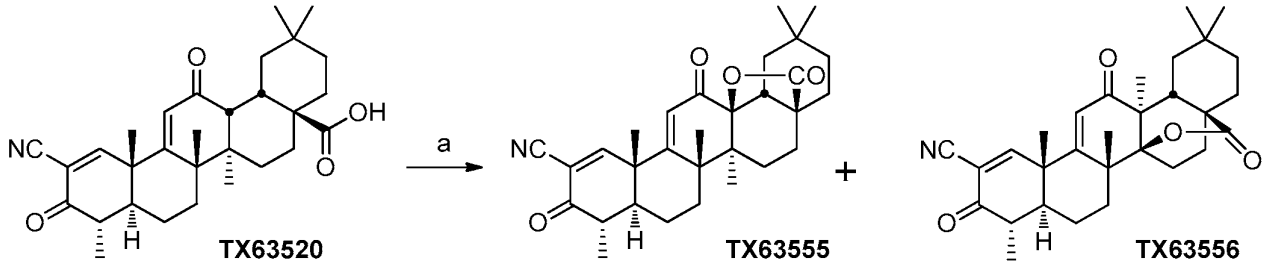
Reagents and conditions: a) (i) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 2 h; (ii) $CF_3CH_2NH_2$, CH_2Cl_2, 0 °C, 90 min, 85%; d) NaOMe, MeOH, 55 °C, 2 h, 81%; e) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 3 h, 86%.

Scheme 8



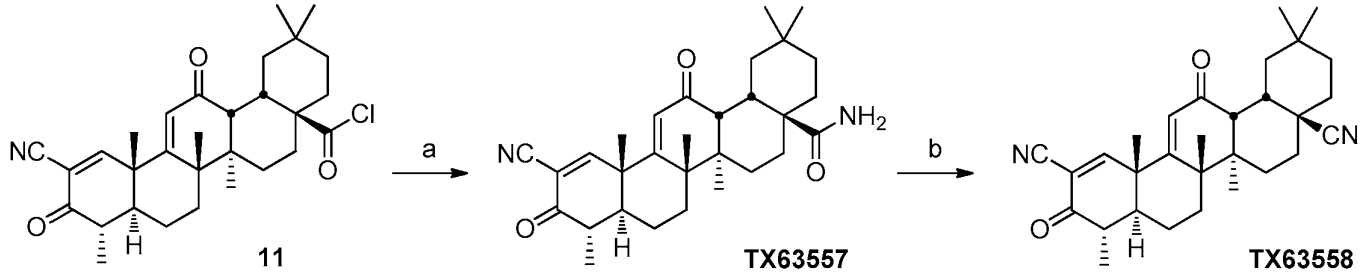
Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 7 h, 59%; b) NBS, DME, H_2O, rt, 30 min, 94%; c) NaOMe, MeOH, 55 °C, 1 h, 94%; d) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 3 h, 80%; e) Ac_2O, Pyridine, CH_2Cl_2, rt, 3 h, 77%.

Scheme 9



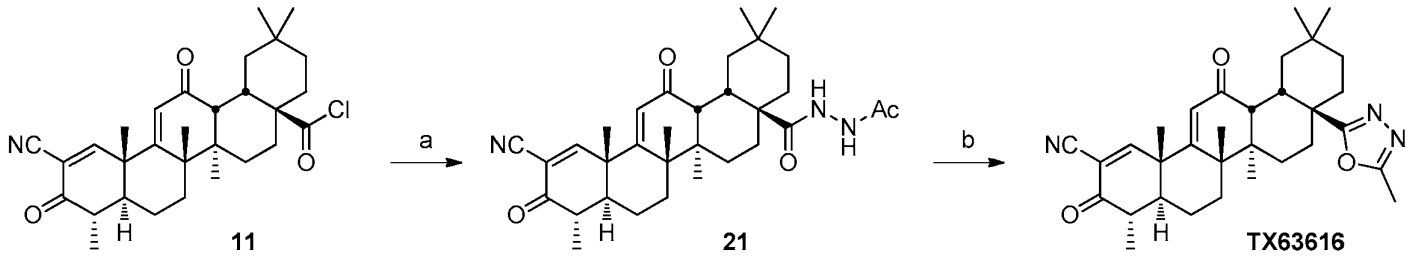
Reagents and conditions: a) IPh(OH)OTs, CH_2Cl_2, reflux, 1 h, 53% for **TX63555**, 37% for **TX63556**.

Scheme 10



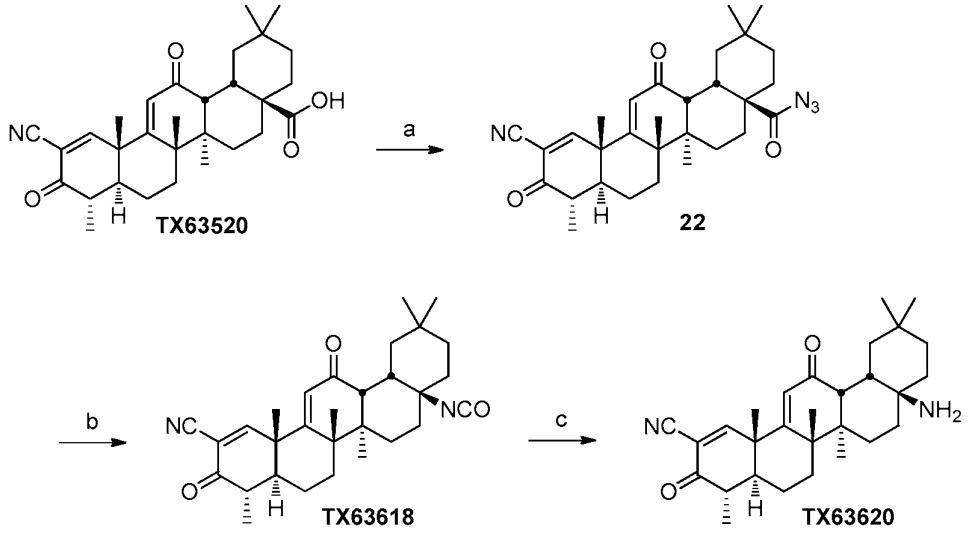
Reagents and conditions: a) NH_3 in MeOH, THF, 0 °C, 30 min, 95%; b) TFAA, Et_3N, CH_2Cl_2, 0 °C, 15 min, 83%.

Scheme 11



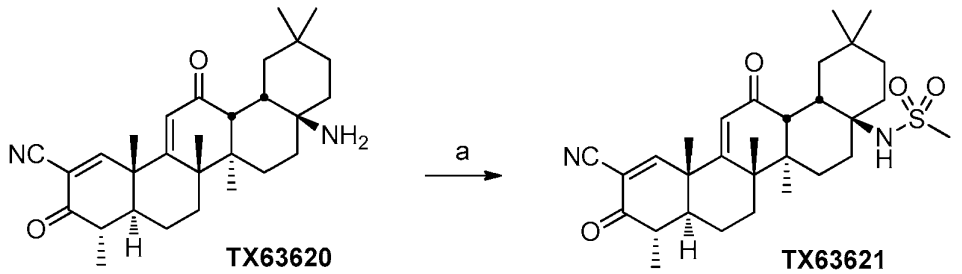
Reagents and conditions: a) $AcNHNH_2$, Et_3N, Et_2O, CH_2Cl_2, 0 °C to rt, 2.5 h, 68%; b) TsOH, toluene, reflux, 2 h, 74%.

Scheme 12



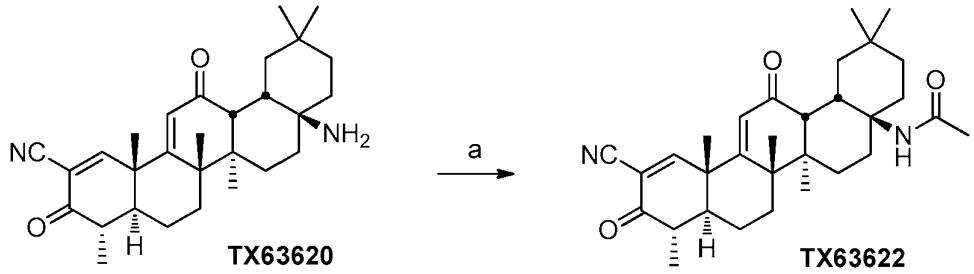
Reagents and conditions: a) DPPA, Et_3N, toluene, 0 °C to rt, 4 h, 79%; b) toluene, 80 °C, 3 hr, 91%; c) MeCN, 12 N HCl, 0 °C ~ rt, 1 h, 97%.

Scheme 13



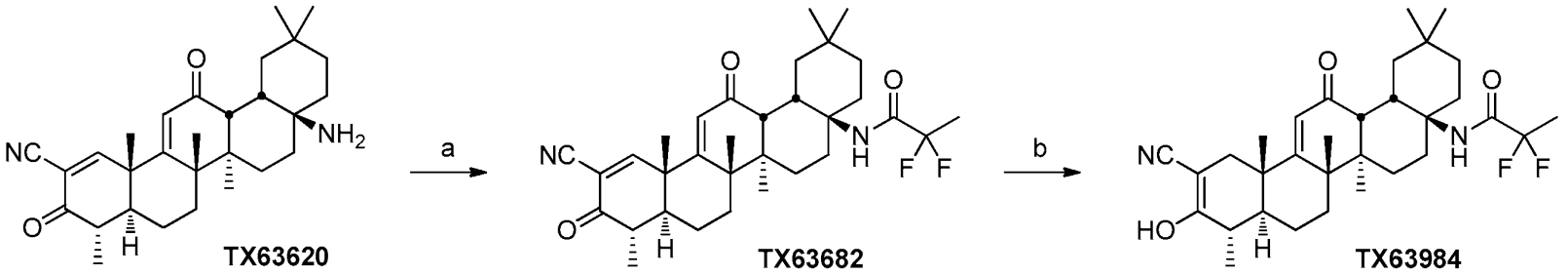
Reagents and conditions: a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 36%.

Scheme 14



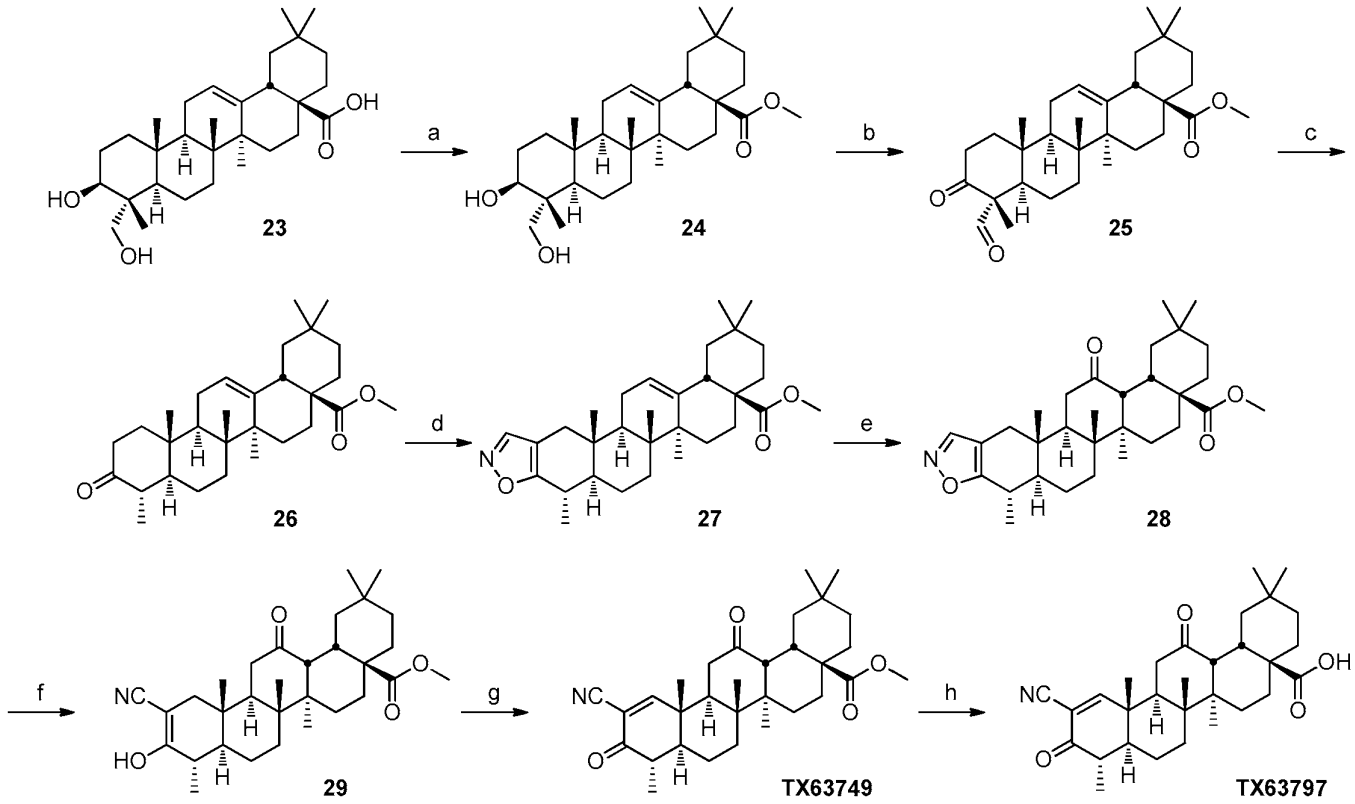
Reagents and conditions: a) CH_3COCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 96%.

Scheme 15



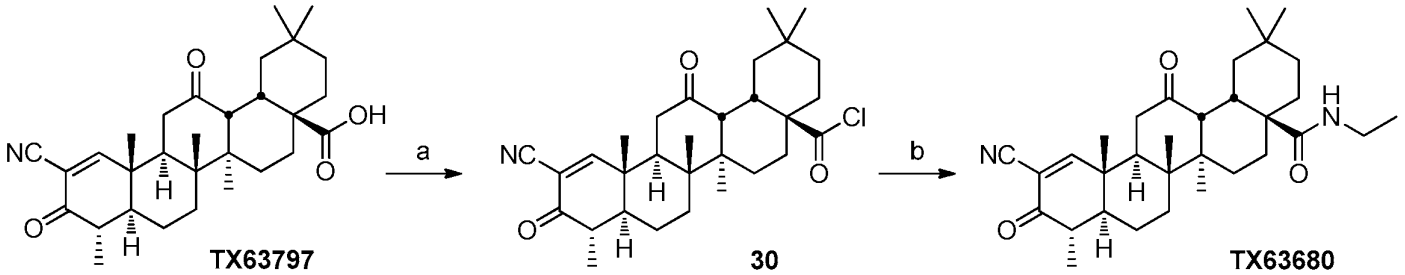
Reagents and conditions: a) CH_3CF_2COOH, DCC, DMAP, CH_2Cl_2, rt, 16 h, 81%; b) H_2, EtOAc, rt, 2 h, 85%.

Scheme 16



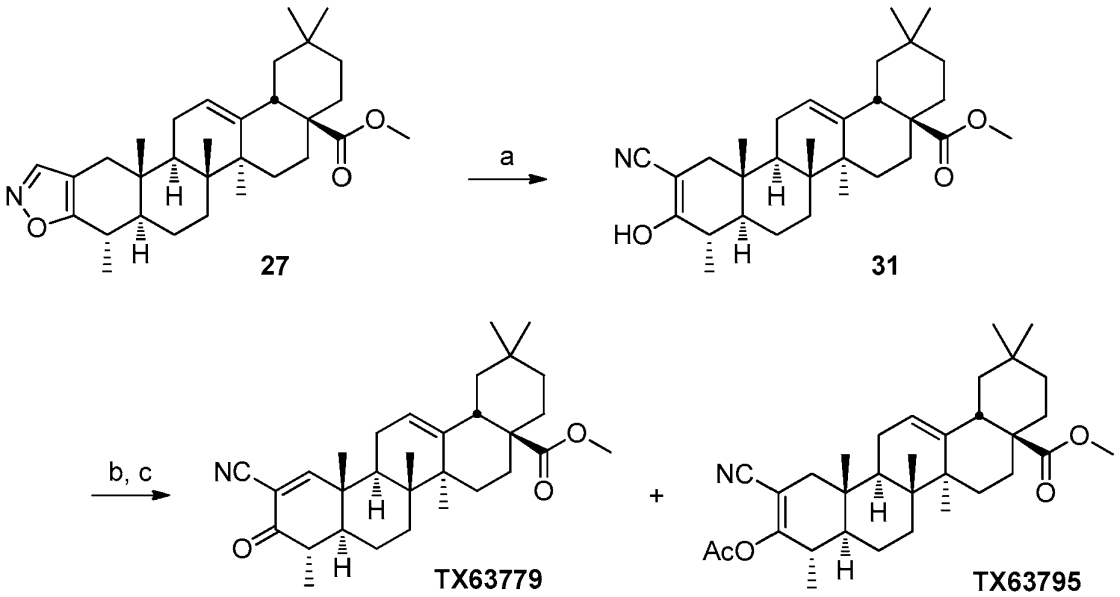
Reagents and conditions: a) $TMSCHN_2$, MeOH, toluene, 0 °C, 1 h, 96%; b) (i) $(COCl)_2$, DMSO, -78 °C, 1.5 h; (ii) Et_3N, rt, 1 h; c) NaOMe, MeOH, rt, 30 min, 76% yield from **24**; d) (i) NaOMe, MeOH, 0 °C to rt, 6 h; (ii) NH_2OH-HCl, 55 °C, 16 h, 83%; e) 39% AcOOH in AcOH, AcOH, 55 °C, 18 h, 80%; f) HCOOEt, NaOMe, MeOH, 55 °C, 1 h; g) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 3 h, 90% from **28**; h) LiBr, NaOAc, DMAc, 150 °C, 6 h, 61%.

Scheme 17



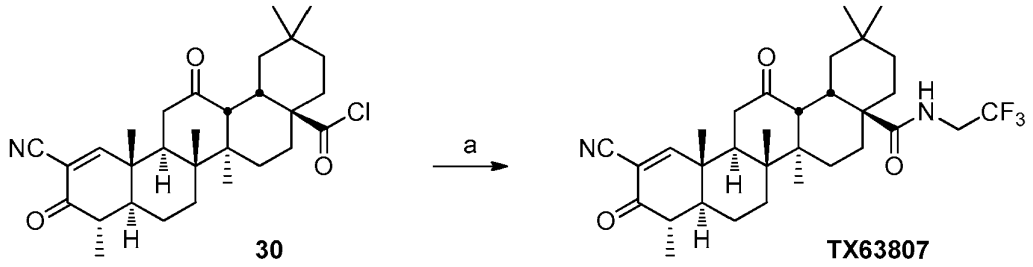
Reagents and conditions: a) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C to rt, 2 h; b) $EtNH_2$, CH_2Cl_2, THF, 0 °C, 30 min, 88%.

Scheme 18



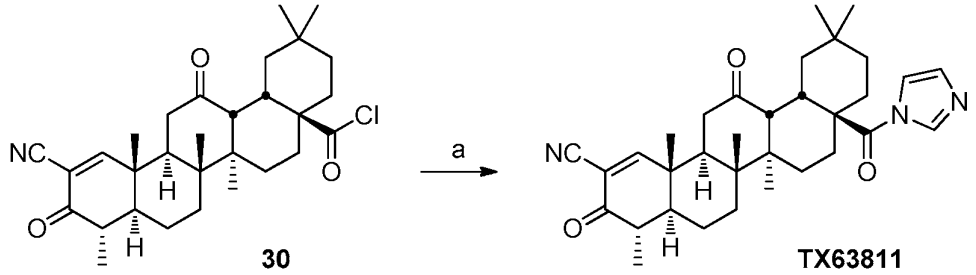
Reagents and conditions: a) NaOMe, MeOH, THF, 55 °C, 2 h, 95%; b) DDQ, benzene; c) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 20 min, 27% for **TX63779** from **27**, 43% for **TX63795** from **27**.

Scheme 19



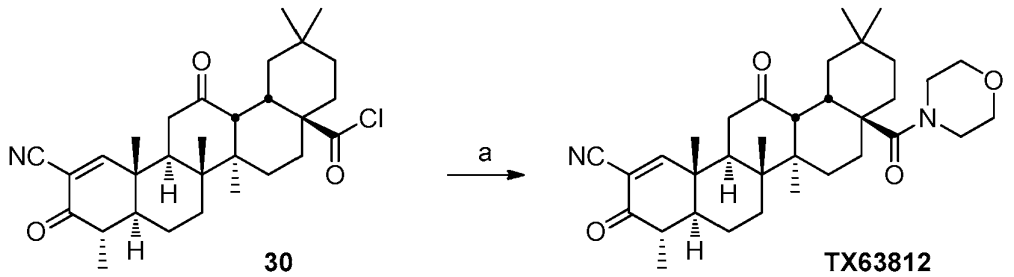
Reagents and conditions: a) $CF_3CH_2NH_2$, CH_2Cl_2, 0 °C-rt, 2 h, 62%.

Scheme 20



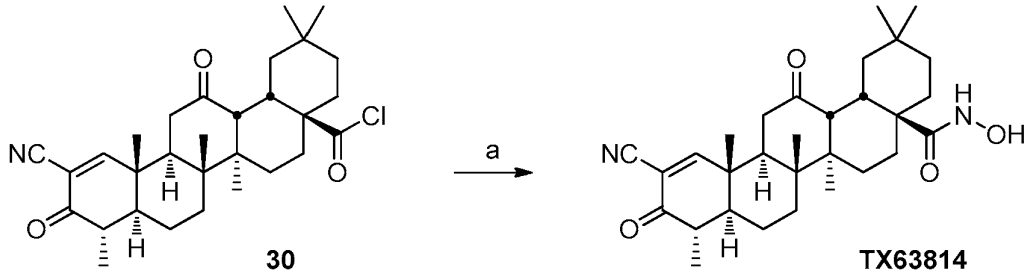
Reagents and conditions: a) imidazole, benzene, 0 °C-rt, 2 h, 80%.

Scheme 21



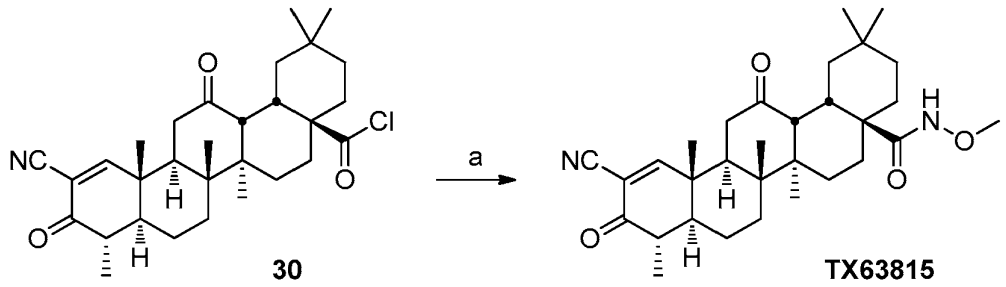
Reagents and conditions: a) morpholine, CH_2Cl_2, 0 °C-rt, 1 h, 68%.

Scheme 22



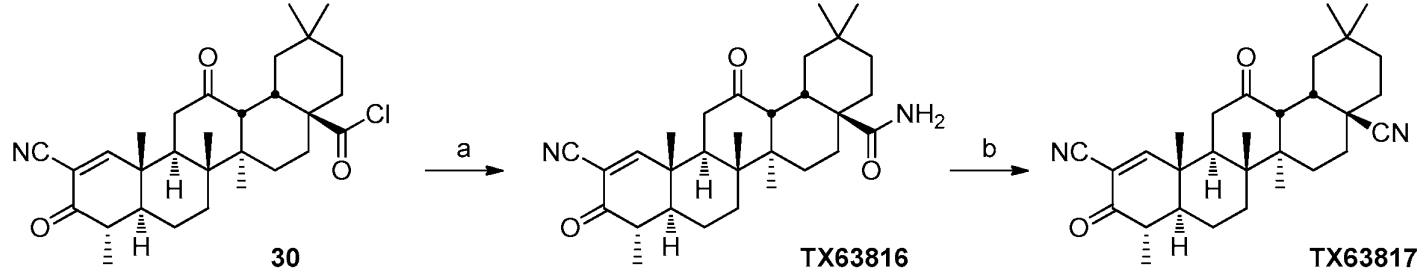
Reagents and conditions: a) NH_2OH-HCl, THF, H_2O, Et_3N, rt, 1 h, 48%.

Scheme 23



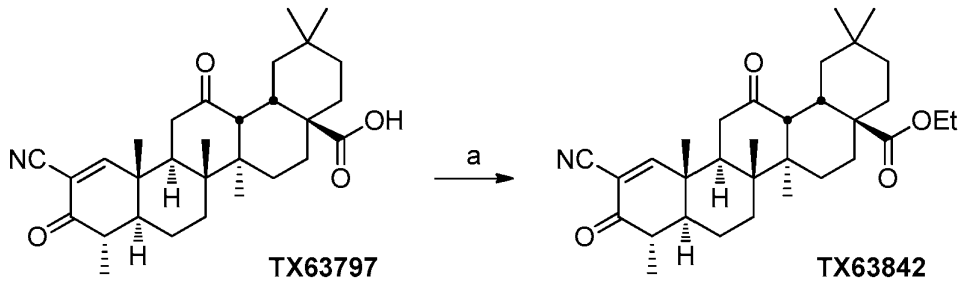
Reagents and conditions: a) NH_2OMe-HCl, THF, H_2O, Et_3N, rt, 1 h, 61%.

Scheme 24



Reagents and conditions: a) NH_3 in MeOH, MTBE, CH_2Cl_2, 0 °C-rt, 1 h, 83%; b) TFAA, Et_3N, CH_2Cl_2, 0 °C, 30 min, 75%.

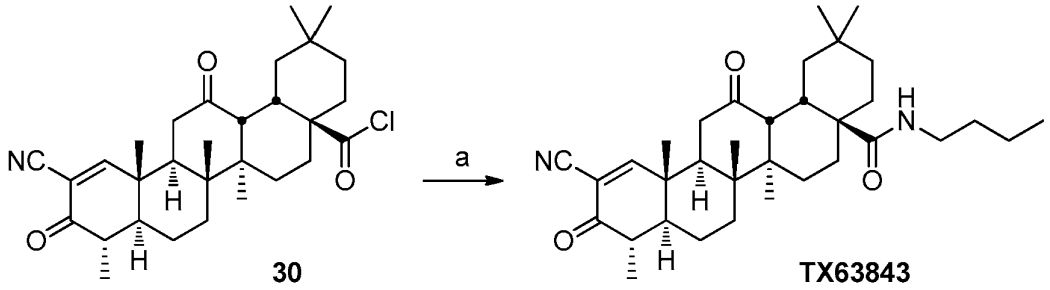
Scheme 25



TX63797 TX63842

Reagents and conditions: a) EtI, DBU, toluene, 50 °C, 2 h, 61%.

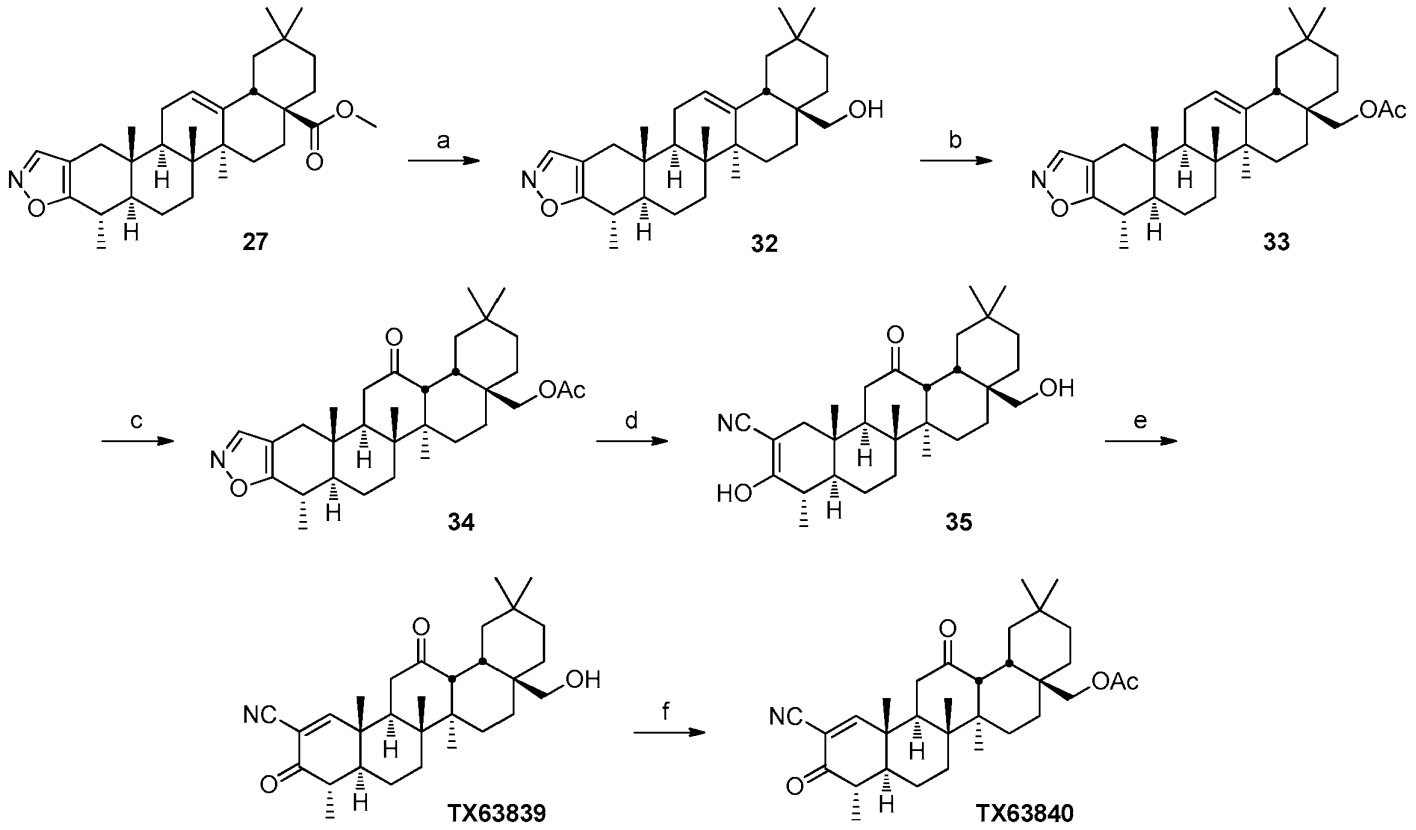
Scheme 26



30 TX63843

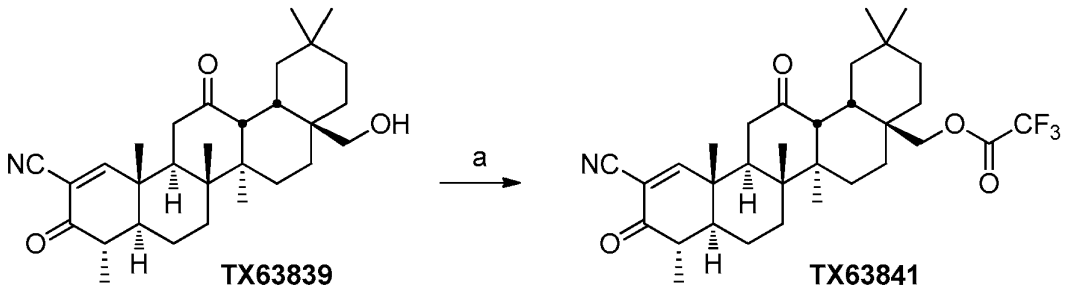
Reagents and conditions: a) *n*-$BuNH_2$, CH_2Cl_2, 0 °C, 30 min, 69%.

Scheme 27



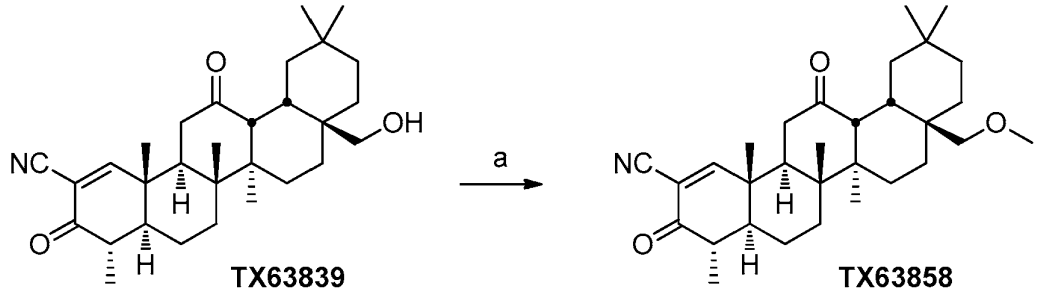
Reagents and conditions: a) DIBAL-H, THF, 0 °C, 2 h, 96%; b) Ac_2O, Pyridine, DMAP, rt, 10 min, 96%; c) AcOOH, AcOH, 55 °C, 20 h, 80%; d) NaOMe, MeOH, 55 °C, 1 h, 99%; e) (i) DBDMH, DMF, 0 °C, 1.5 h; (ii) pyridine, 55 °C, 1.5 h, 81%; f) Ac_2O, Pyridine, DMAP, CH_2Cl_2, rt, 10 min, 99%.

Scheme 28



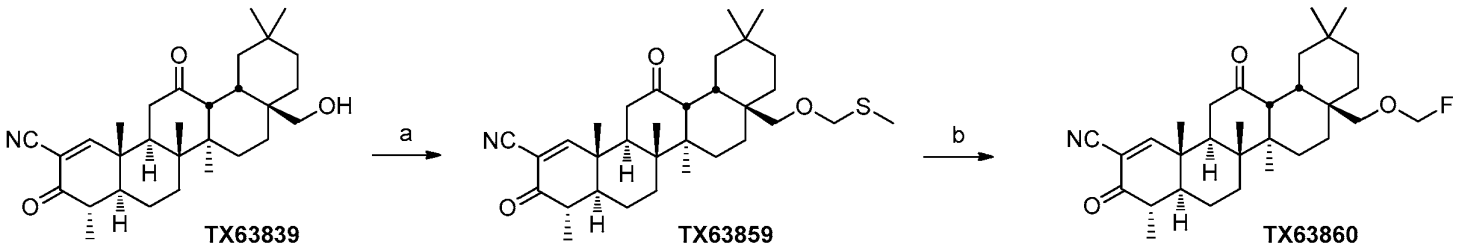
Reagents and conditions: a) TFAA, Et_3N, CH_2Cl_2, 0 °C, 1 h, 87%.

Scheme 29



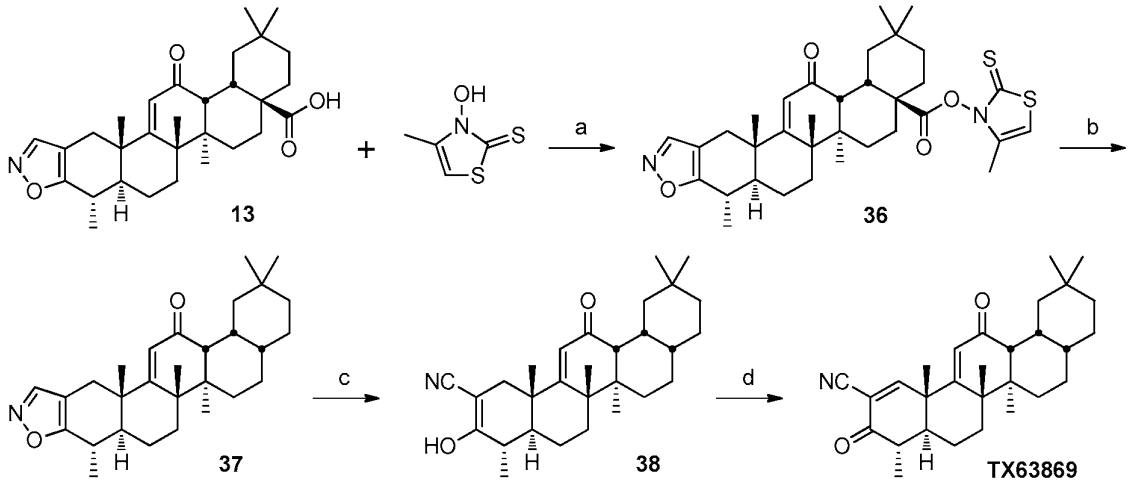
Reagents and conditions: a) MeOTf, 2,6-di-t-butyl-4-methylpyridine, CH_2Cl_2, rt, 16 h, 75%.

Scheme 30



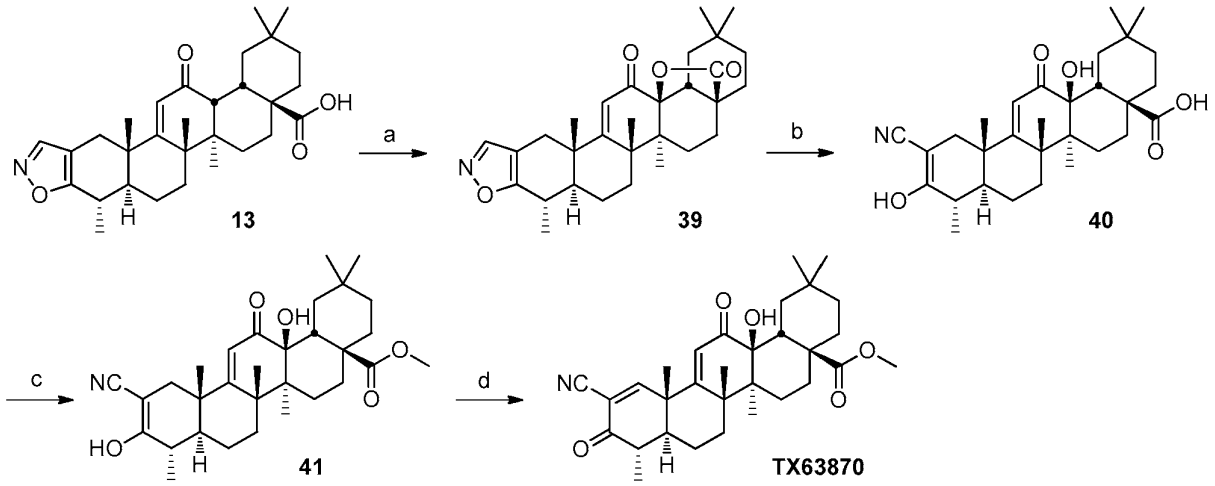
Reagents and conditions: a) DMSO, AcOH, Ac_2O, rt, 20 h, 80%; b) DAST, NBS, 4Å MS, CH_2Cl_2, 0 °C, 50 min, 52%.

Scheme 31



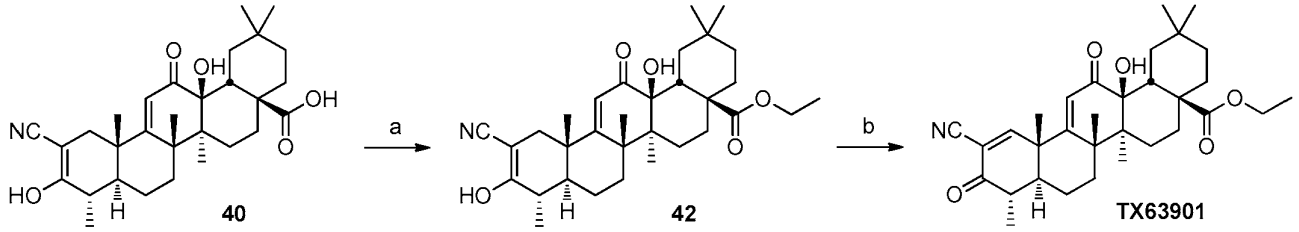
Reagents and conditions: a) DCC, DMAP, CH_2Cl_2, rt, 5 h, 80%; b) Bu_3SnH, AIBN, benzene, reflux, 25 min, 89%; c) NaOMe, MeOH, 55 °C, 2 h, 99%; d) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 2 h, 84%.

Scheme 32



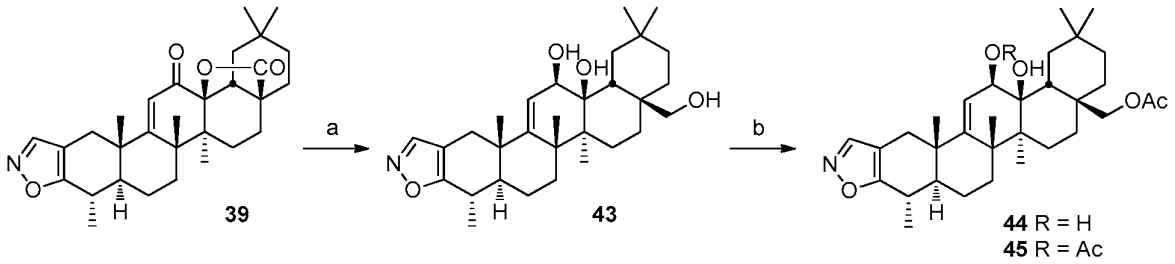
Reagents and conditions: a) DDQ, toluene, microwave, 115 °C, 3 h, 47%; b) NaOH, THF, EtOH, H_2O, rt, 6 h; c)$TMSCHN_2$, toluene, MeOH, -20 °C, 15 min, 42% for 2 steps; d) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 2 h, 72%.

Scheme 33



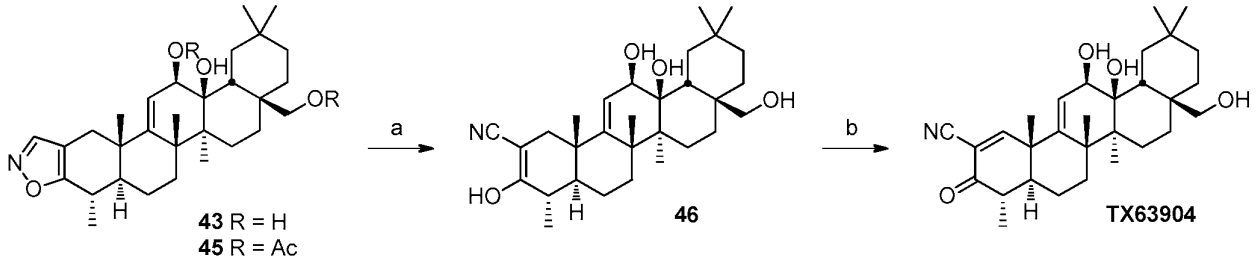
Reagents and conditions: a) CH_3CHN_2, $CHCl_3$, MTBE, 0 °C, 15 min, 18%; b) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 2 h, 68%.

Scheme 34



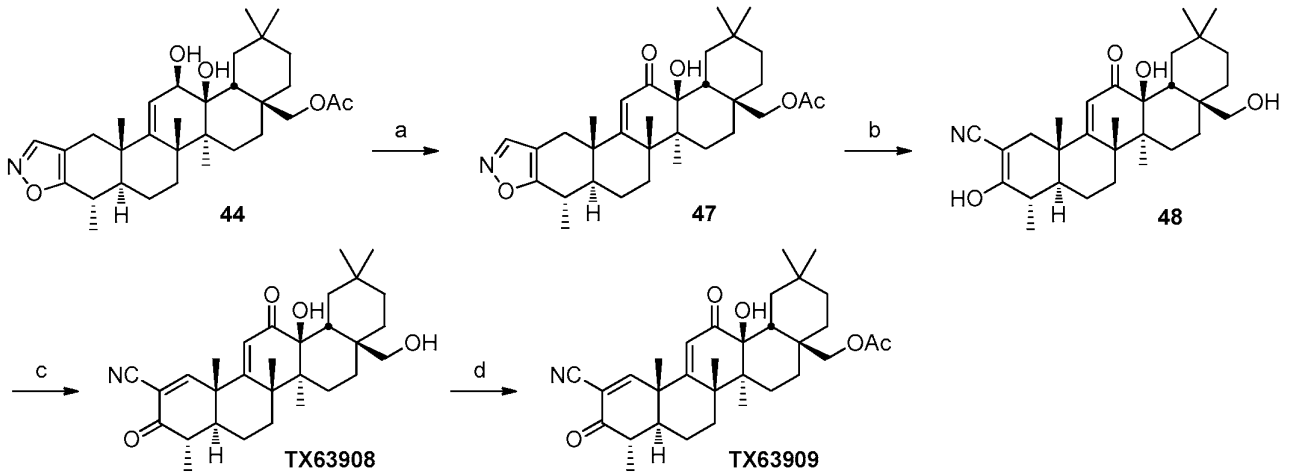
Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 3 h, 47%; b) Ac_2O, Pyridine, DMAP, CH_2Cl_2, 0 °C, 1 h, 75% for **44**.

Scheme 35



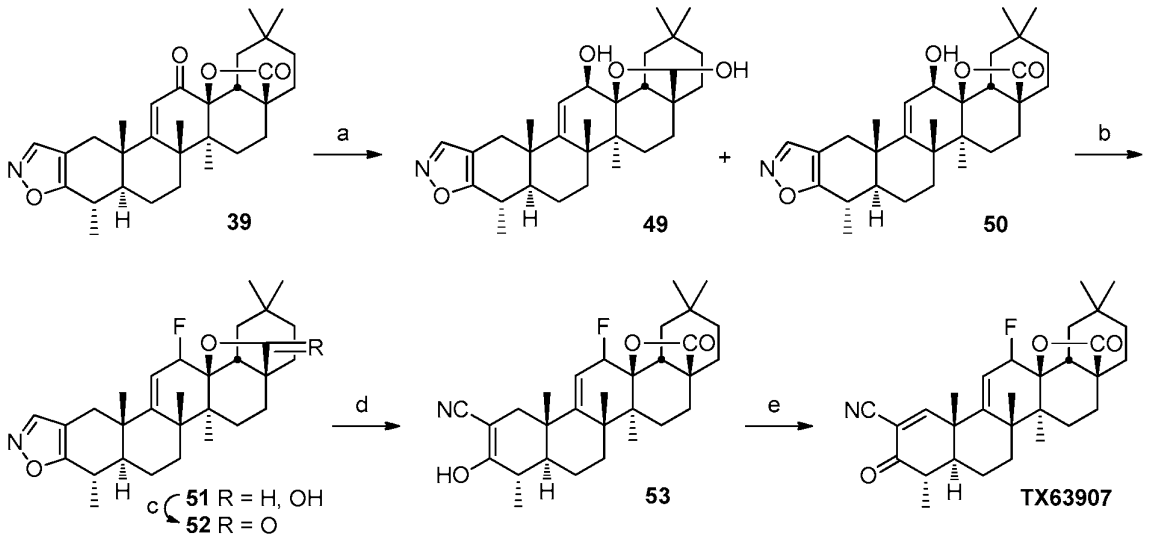
Reagents and conditions: a) NaOMe, MeOH, 55 °C, 1 h, 60%; b) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 2 h, 88%.

Scheme 36



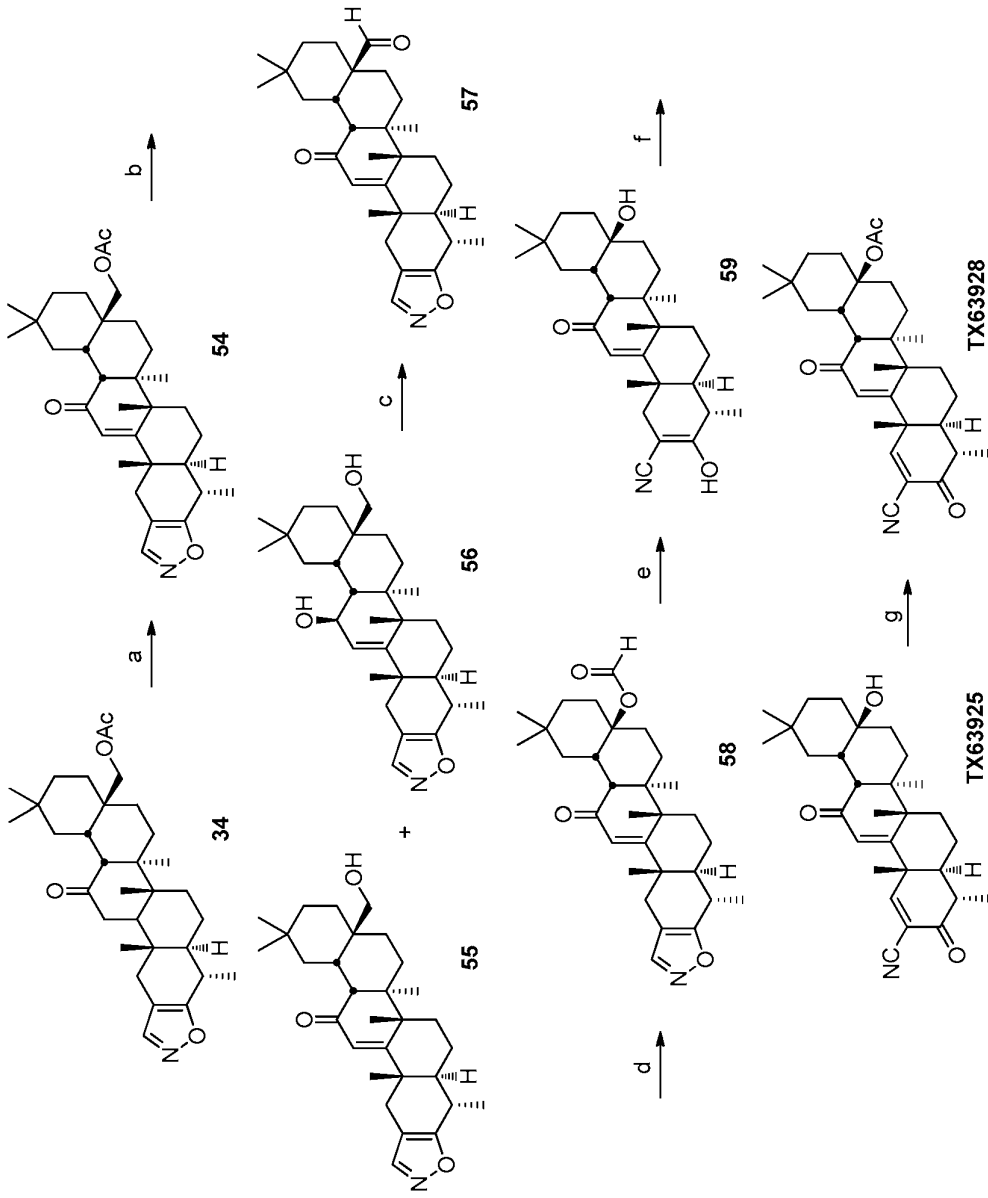
Reagents and conditions: a) NMO, TPAP, 4Å MS, CH_2Cl_2, rt, 3 h, 72%; b) NaOMe, MeOH, 55 °C, 2 h, 89%; c) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 1.5 h, 86%; d) Ac_2O, Pyridine, DMAP, rt, 30 min, 94%.

Scheme 37



Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 1 h, 72%; b) (i) DAST, CH_2Cl_2, 0 °C, 20 min; (ii) silica gel; c) Jones' reagent, acetone, 0 °C, 10 min, 39% from **49** and **50**; d) NaOMe, MeOH, 55 °C, 2 h; e) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 1.5 h, 81% from **52**.

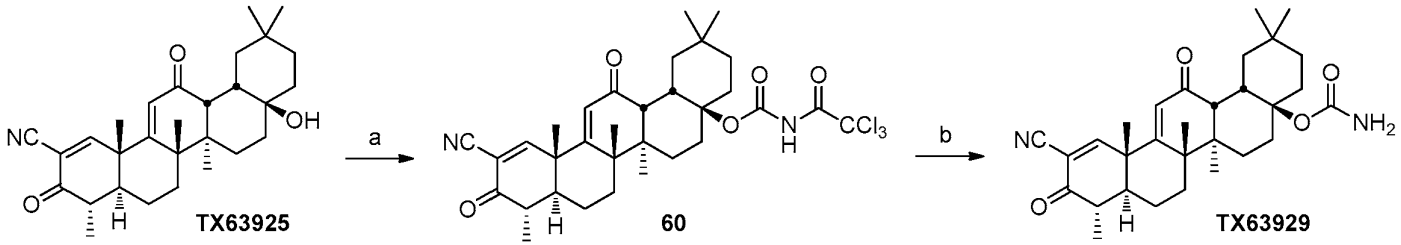
Scheme 38



Reagents and conditions: a) $PyH^{+}Br_3^{-}$, MeCN, rt, 3 h, 66%; b) $LiAlH_4$, THF, 0 °C, 1 h, 46% for **55**, 46% for **56**; c) NMO, TPAP, 4 Å MS,

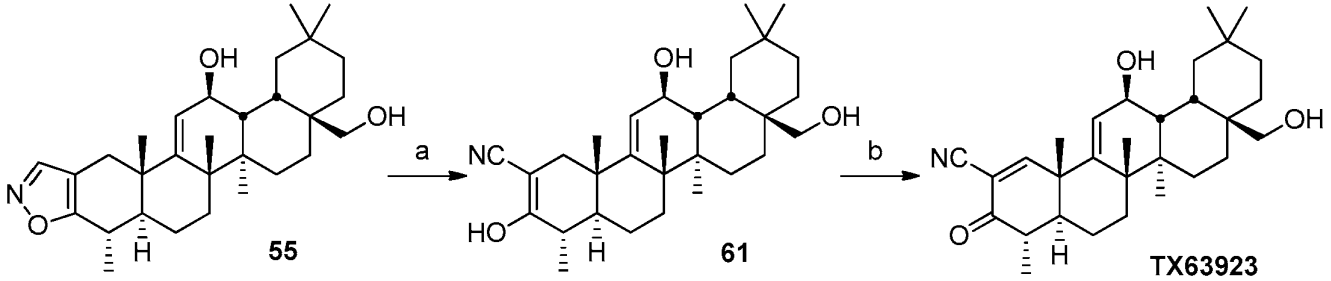
CH_2Cl_2, rt, 1 h, 86%; d) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, rt, 6 h, 85%; e) NaOMe, MeOH, 55 °C, 1 h, 90%; f) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 3 h, 94%; g) Ac_2O, BF_3-OEt_2, CH_2Cl_2, 0 °C, 10 min, 34%.

Scheme 39



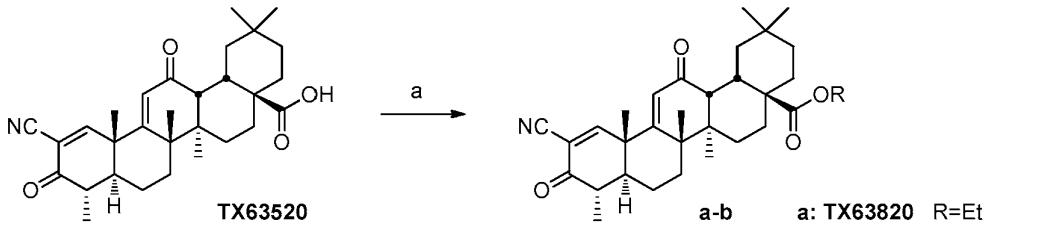
Reagents and conditions: a) $Cl_3CCONCO$, CH_2Cl_2, rt, 2 h; b) K_2CO_3, MeOH, rt, 1 h, 61% for 2 steps.

Scheme 40



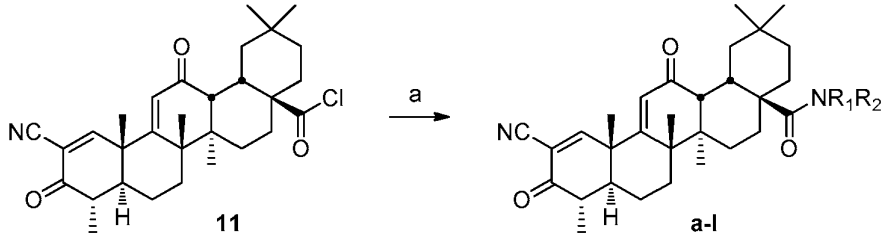
Reagents and conditions: a) NaOMe, MeOH, 55 °C, 1 h, 81%; b) (i) DBDMH, DMF, 0 °C, 1 h; (ii) Pyridine, 55 °C, 3 h, 80%.

Scheme 41



Reagents and conditions: a) alkyl iodide (RI), DBU, Toluene, **TX63820:** rt, 21 h, 18.4%; **TX63821:** rt, 18 h, then 80 °C, 2 h, 75%.

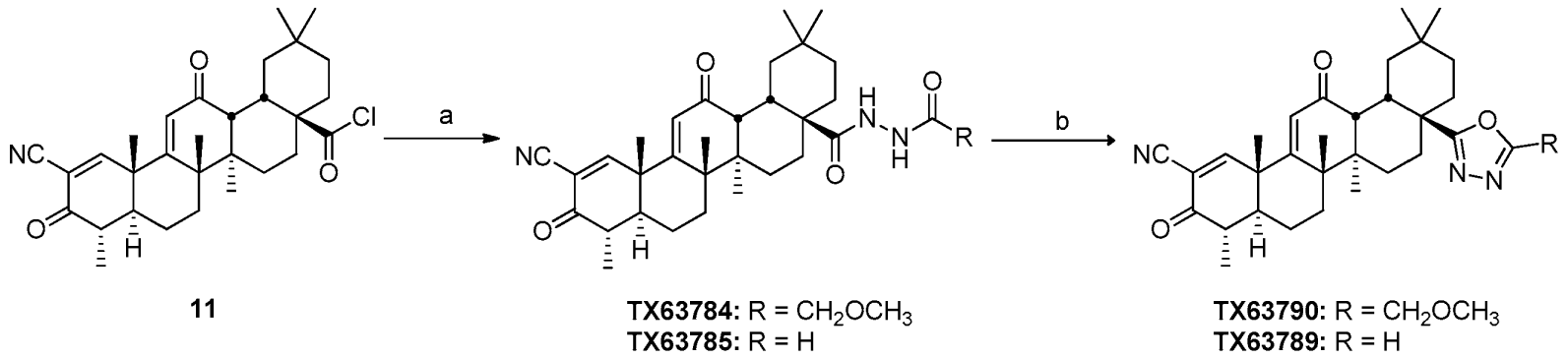
Scheme 42



a: TX63878 NR_1R_2=NMe_2
b: TX63824 NR_1R_2=NHMe
c: TX63877 NR_1R_2=NH-*n*-C_4H_9
d: TX63823 NR_1R_2=1-pyrrolidinyl
e: TX63880 NR_1R_2=1-piperidinyl
f: TX63881 NR_1R_2=4-morpholinyl
g: TX63822 NR_1R_2=2,4-dimethyl-1H-imidazol-1-yl
h: TX64005 NR_1R_2=methyl 5-carboxylate-1H-imidazol-1-yl
i: TX63882 NR_1R_2=NHOMe
j: TX64006 NR_1R_2=NHOH
k: TX63825 NR_1R_2=*N*-3-oxetanyl
l: TX64007 NR_1R_2=2-oxa-6-azaspiro[3.3]hept-6-yl

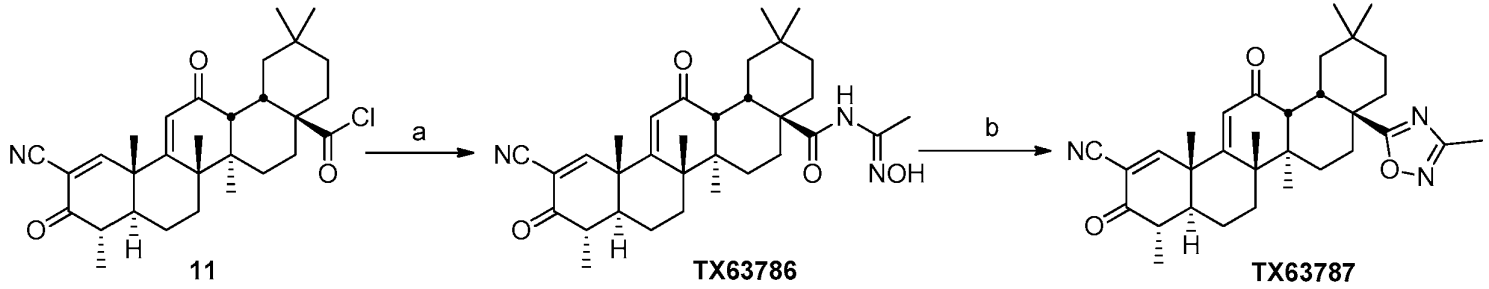
Reagents and conditions: a) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt, 2 h; (b) R_1R_2NH, reaction conditions: see experimental for details.

Scheme 43



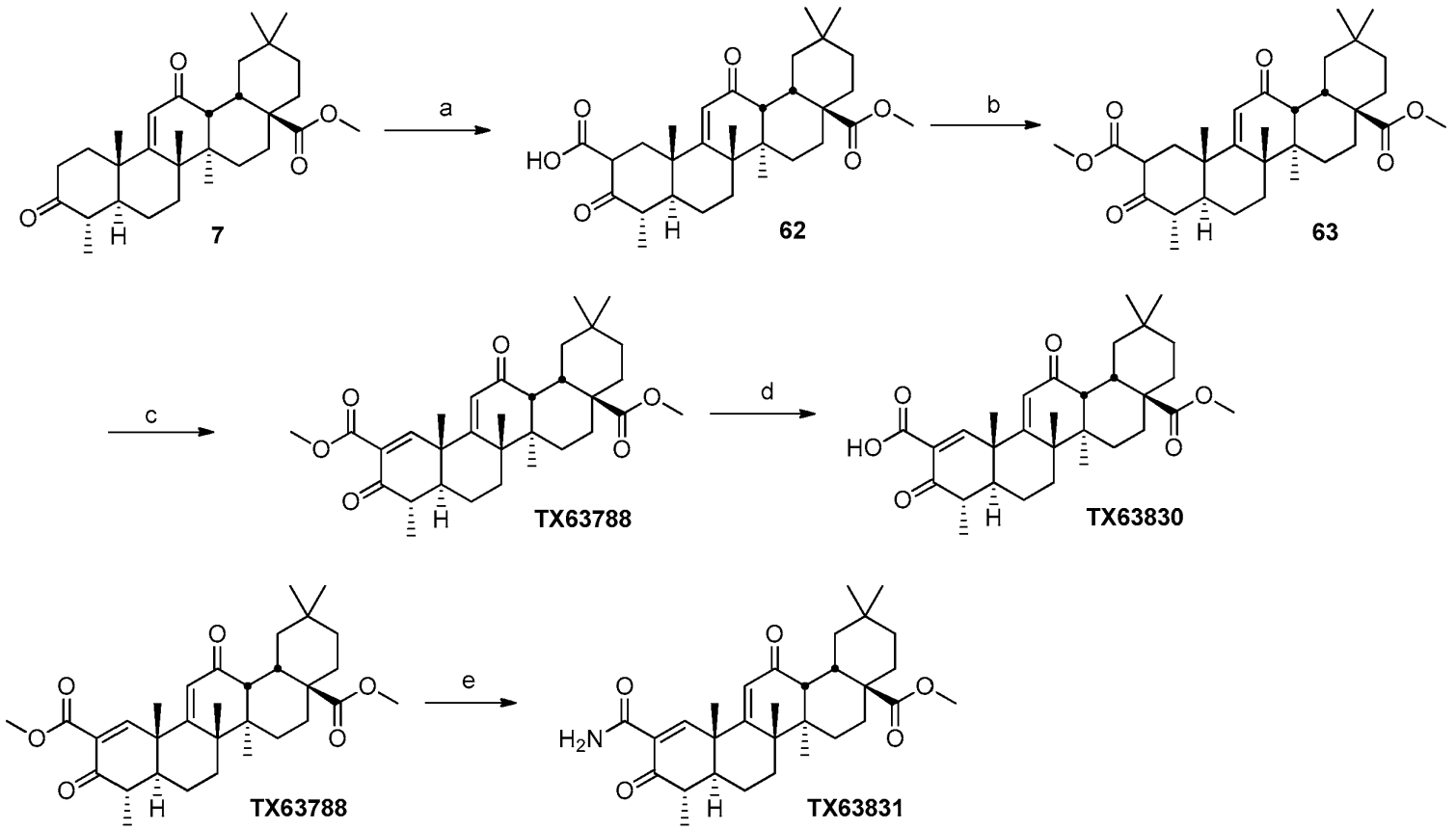
Reagents and conditions: a) $H_2NNHCOR$, DCM, TEA, rt, **TX63784**: 72%, **TX63785**: 47%; b) TsOH-H_2O, Toluene, reflux, -H_2O, **TX63789**: 34%, **TX63790**: 51%.

Scheme 44



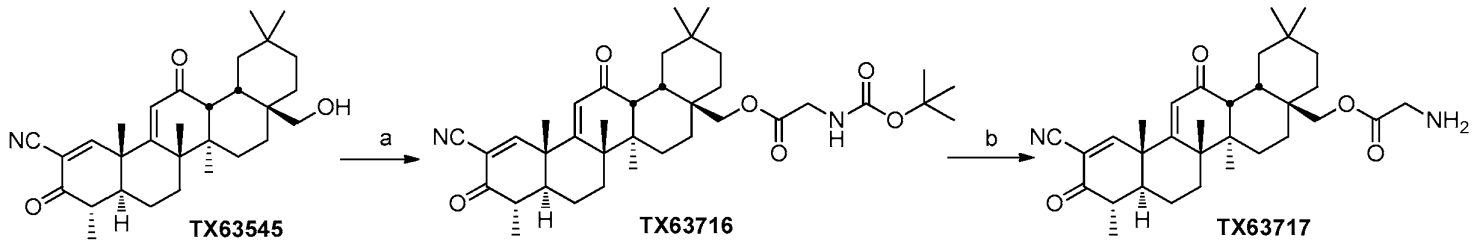
Reagents and conditions: a) Acetamide oxime, DCM, TEA, rt, 61%; b) EtOAc, Toluene, 200 °C, microwave, 20 min, 24%.

Scheme 45



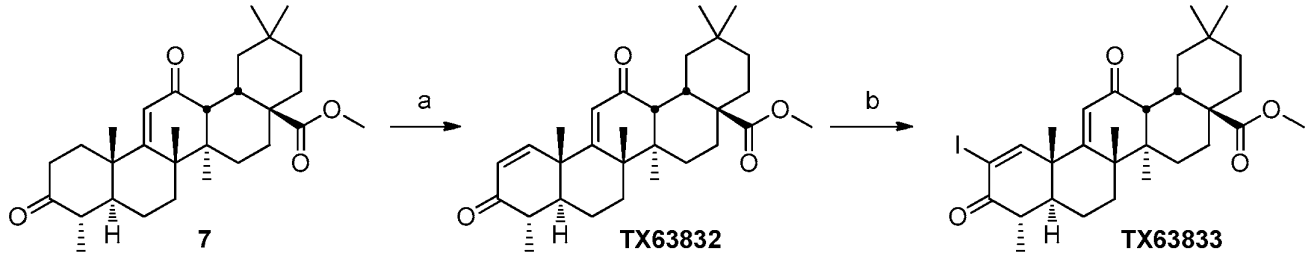
Reagents and conditions: a) MMC, DMF, 110°C, N_2 sparge, 99%; b) $TMSCHN_2$, THF, MeOH, 0°C; c) (i) PhSeCl, pyridine, DCM, 0°C; (ii) H_2O_2, 0°C, 67% ; d) KOH, H_2O, MeOH, reflux, 61%; e) NH_3, MeOH, rt, 40%.

Scheme 46



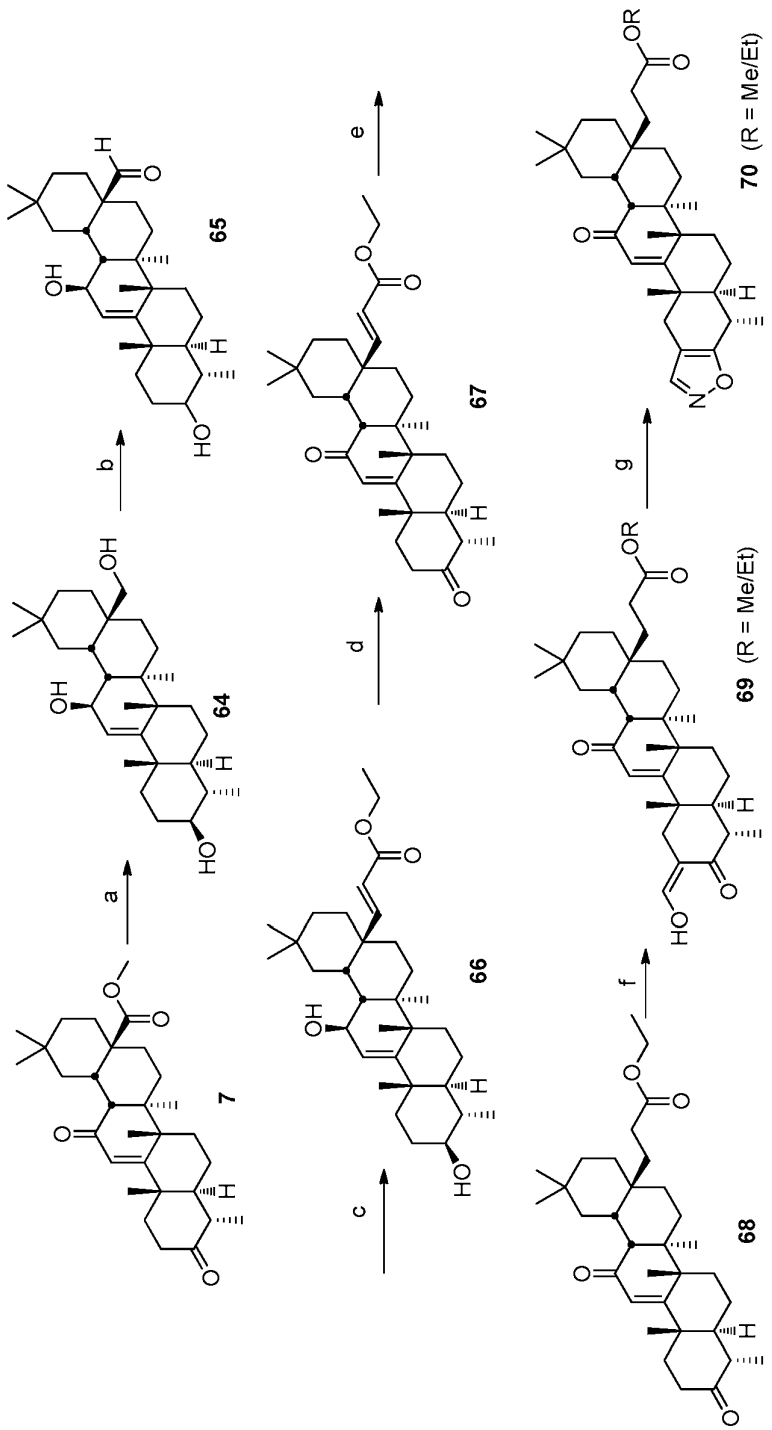
Reagents and conditions: a) N-Boc-Gly-OH, EDC, DMAP, DCM, rt, 85%; b) HCl, DCM, 1,4-dioxane, rt, 85%.

Scheme 47

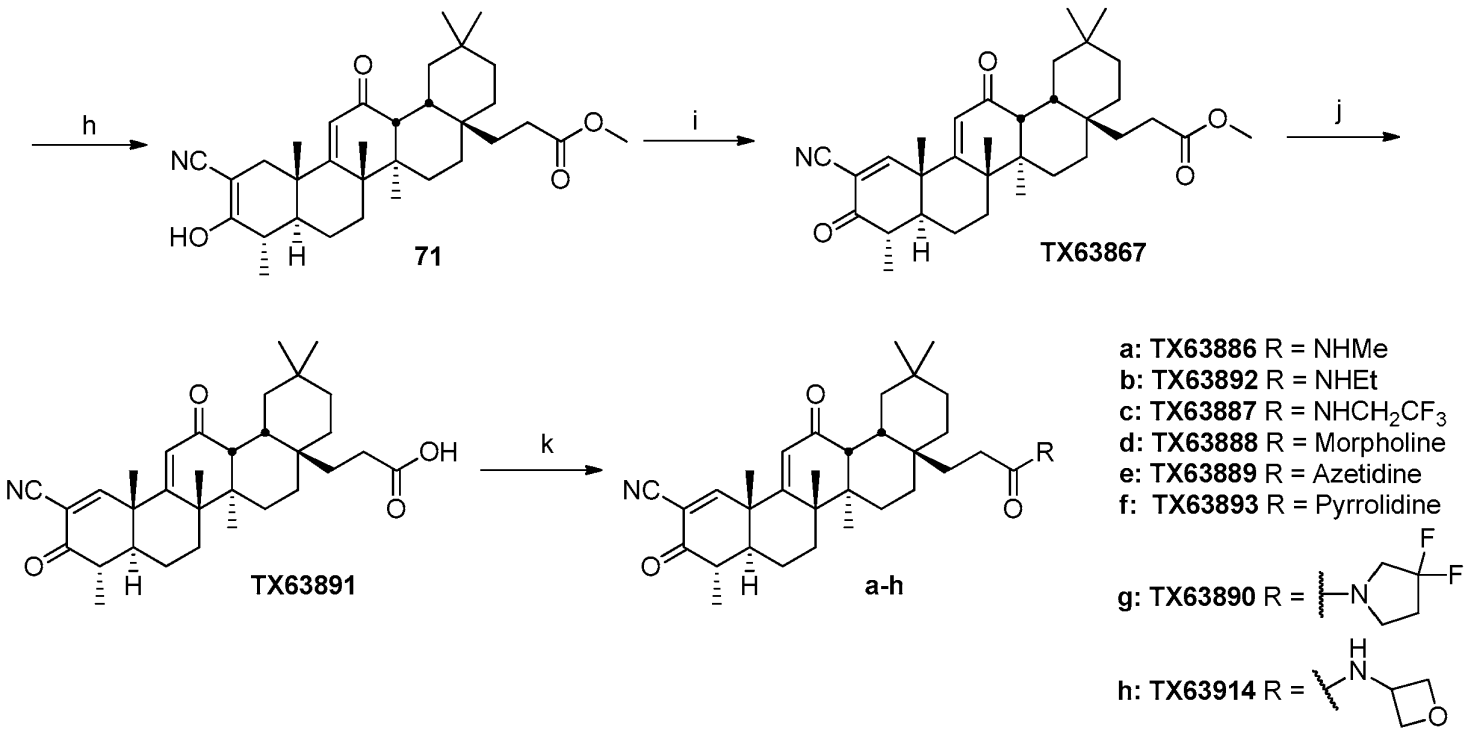


Reagents and conditions: a) (i) PhSeCl, EtOAc, rt to -20 °C; (ii) H_2O_2, THF, rt, 55%; b) I_2, pyridine THF, reflux, 60%.

Scheme 48 (a)

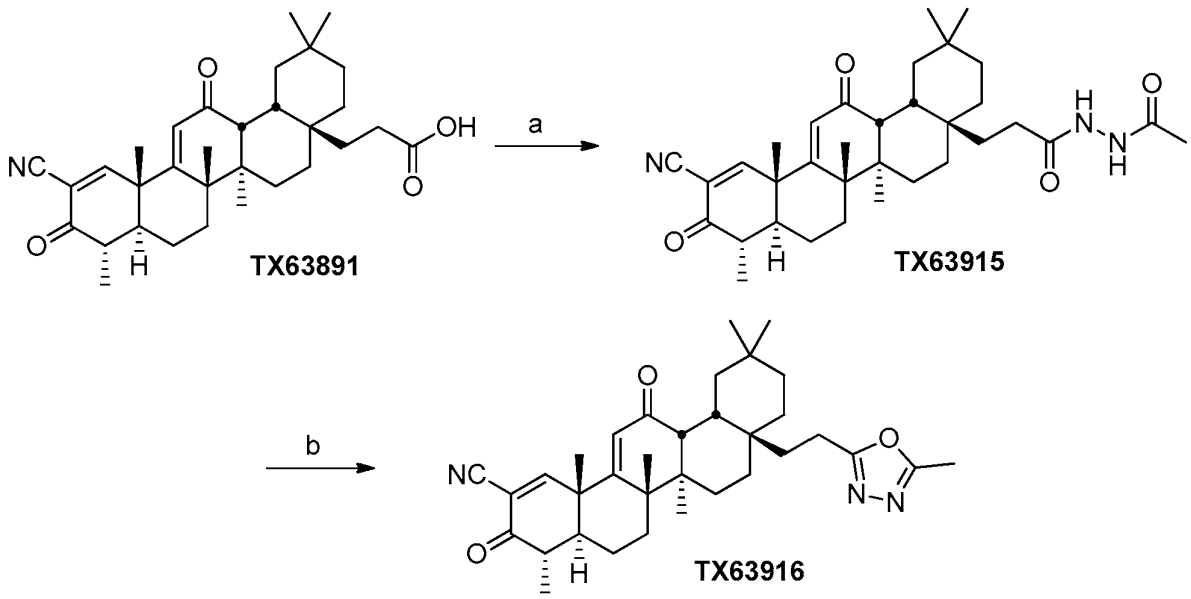


Scheme 48 (b)



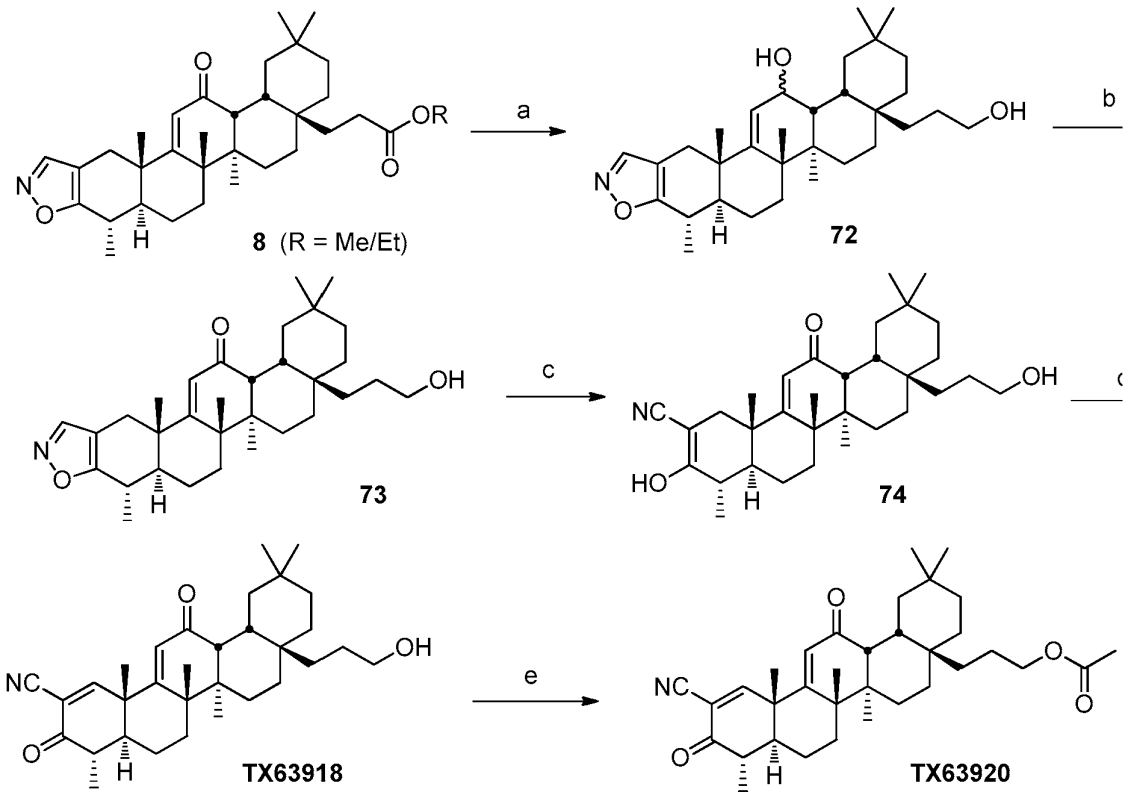
Reagents and conditions: a) LAH, THF, 0 °C to rt; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, H_2O, rt, 27%; c) Triethyl phosphonoacetate, NaH, 0 °C to rt, 67%; d) TPAP, NMO, CH_2Cl_2, 4 AMS, rt, 88%; e) Pd/C, H_2, THF, rt; f) EtOCHO, NaOMe, MeOH, rt; g) (i) NH_2OH•HCl, EtOH, H_2O, 55 °C, (ii) HCl, MeOH, rt, 80%; h) NaOMe, MeOH, 55 °C; i) (i) DBDMH, DMF, 0 °C, (ii) pyridine, 55 °C, 82%; j) HCl, H_2O, MeCN, 65 °C, 93%; k) amine or amine-HCl, EDCI, TEA, DMAP, CH_2Cl_2, rt, **TX63888**: 69%, **TX63893**: 74%, **TX63886**: 76%, **TX63887**: 77%, **TX63889**: 84%, **TX63890**: 79%, **TX63892**: 85%, **TX63914**: 75%.

Scheme 49



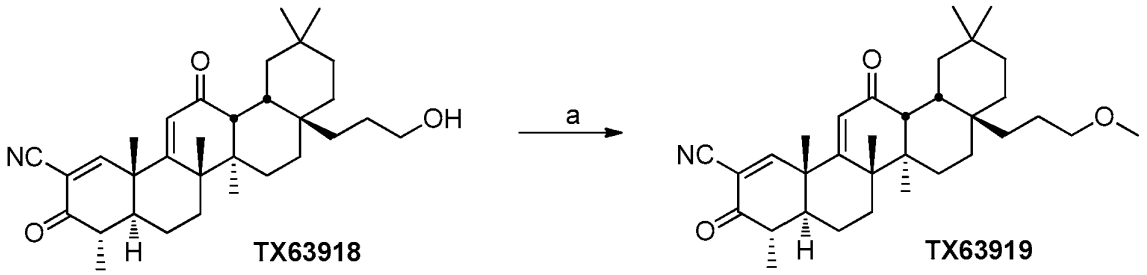
Reagents and conditions: a) $AcNHNH_2$, EDC, TEA, DMAP, DCM, rt, 74%; b) $TsOH\text{-}H_2O$, toluene, reflux, $-H_2O$, 73%.

Scheme 50



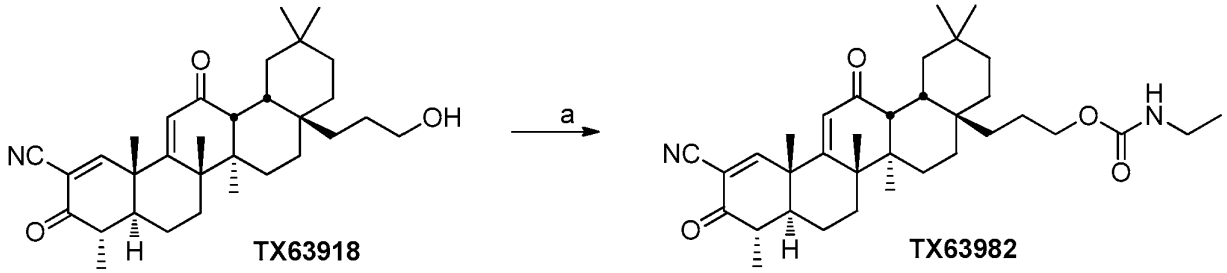
Reagents and conditions: a) DIBAL-H, THF, 0 °C to rt; b) NBS, DME, H2O, rt, 81%; c) NaOMe, MeOH, rt, 67%; d) DBDMH, DMF, 0 °C; then Pyridine, 55 °C, 83%; e) Ac_2O, TEA, DMAP, DCM, rt, 95%.

Scheme 51



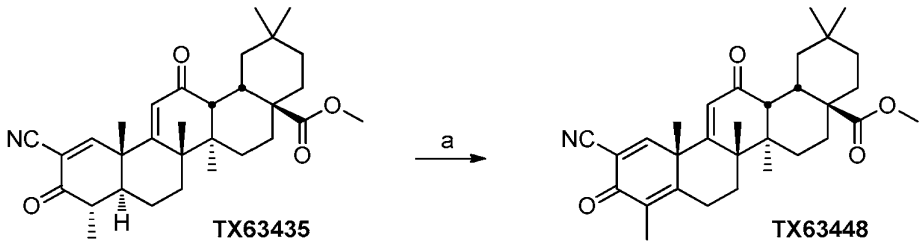
Reagents and conditions: a) MePTf, 2,6-tBu-4-Me-Pyridine, DCM, rt, 73%.

Scheme 52



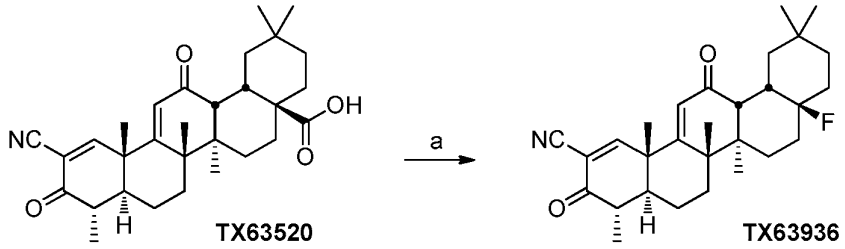
Reagents and conditions: a) EtNCO, toluene, rt, 73%.

Scheme 53



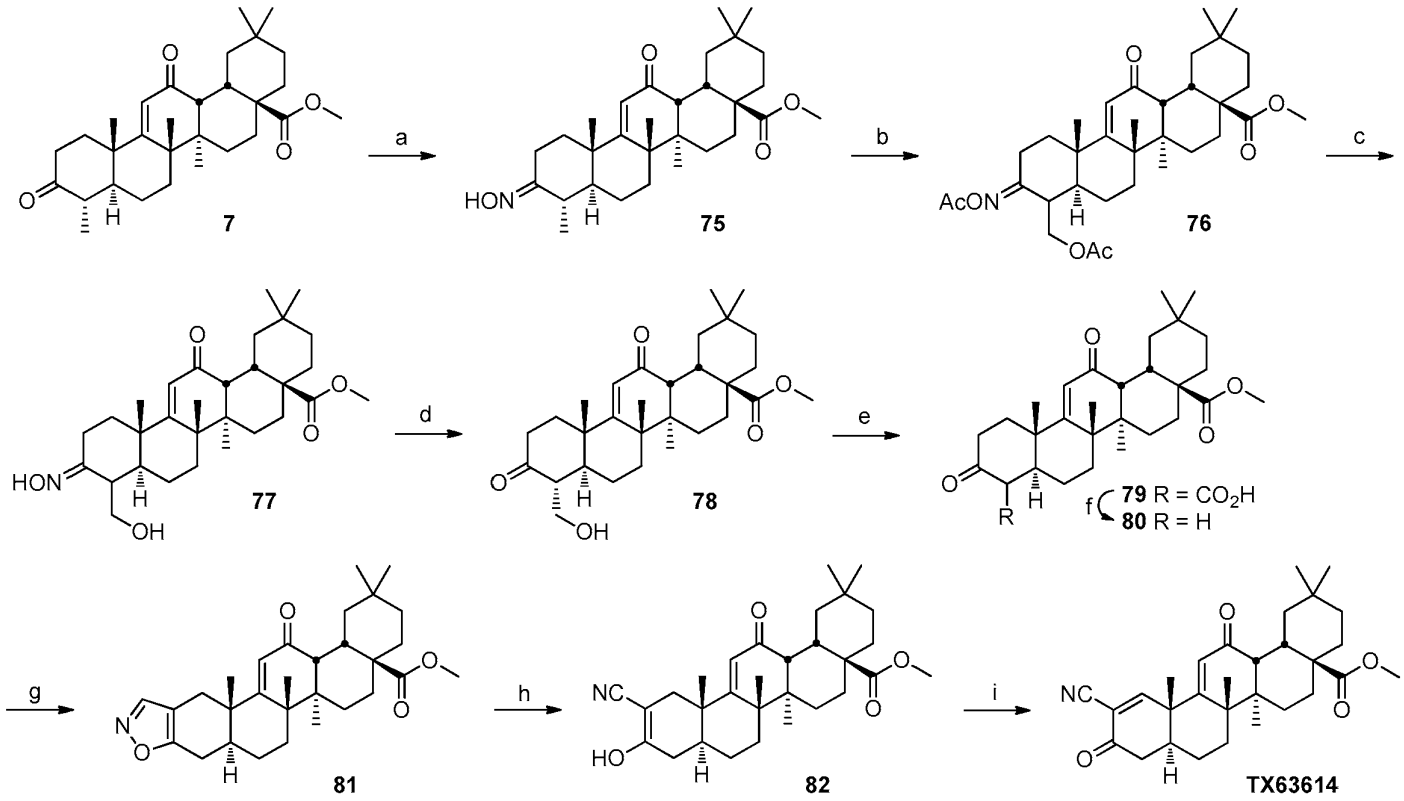
Reagents and conditions: a) SeO_2, 1,4-dioxane, 12%.

Scheme 54



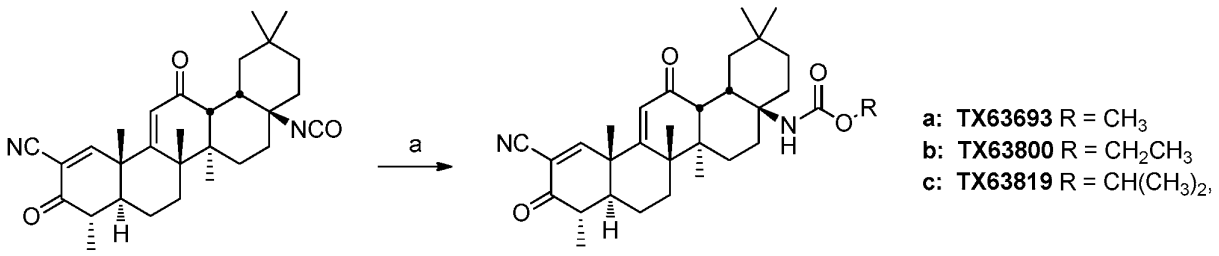
Reagents and conditions: a) XeF_2, CH_2Cl_2, rt, 16 h, 9%.

Scheme 55



Reagents and conditions: a) NH_2OH-HCl, NaOAc, CH_2Cl_2, MeOH, 60 °C, 1.5 h; b) i) AcOH, Ac_2O, rt, 1 h; ii) $PhI(OAc)_2$, $Pd(OAc)_2$, $ClCH_2CH_2Cl$, 60 °C, 15 h, then 80 °C, 6 h, 44% from **7**; c) K_2CO_3, MeOH, 0 °C-rt, 1.5 h; d) $NaHSO_3$, aq. EtOH, 80 °C, 4 h, 73% from **78**; e) Jones' reagent, 0 °C; f) 80 °C, 2 h, then, 120 °C, 30 min, vacuum, 80% from **81**; g) i) HCO_2Et, NaOMe, 0 °C-rt, 5 h; ii) NH_2OH-HCl, aq. EtOH, 55 °C, 18 h, 45%; h) NaOMe, MeOH, 55 °C, 3.5 h, 51%; i) DBDMH, DMF, 0 °C, 1 h; Py, 55 °C, 3 h, 81%.

Scheme 56

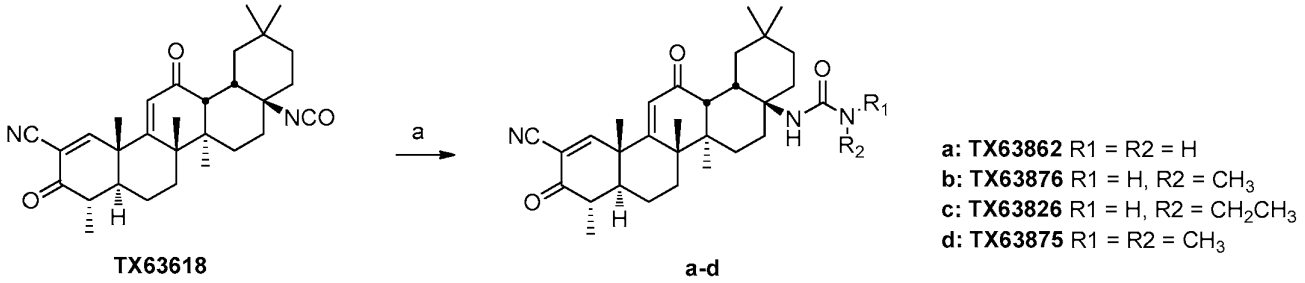


TX63618 **a-c**

a: TX63693 R = CH_3
b: TX63800 R = CH_2CH_3
c: TX63819 R = $CH(CH_3)_2$,

Reagents and conditions: a) ROH, Benzene, 85 °C, 20 hr.

Scheme 57

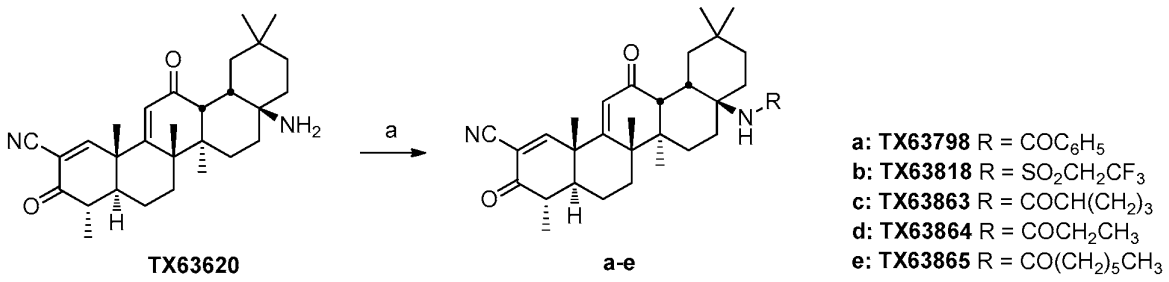


TX63618 **a-d**

a: TX63862 R1 = R2 = H
b: TX63876 R1 = H, R2 = CH_3
c: TX63826 R1 = H, R2 = CH_2CH_3
d: TX63875 R1 = R2 = CH_3

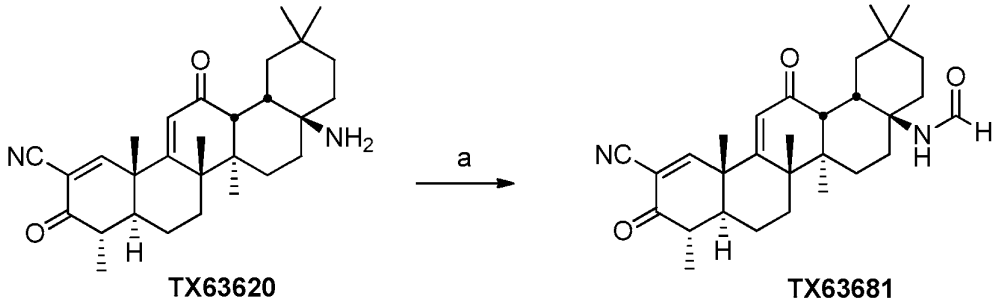
Reagents and conditions: a) R_1R_2NH, THF, 0 °C to rt, 2-20 h.

Scheme 58



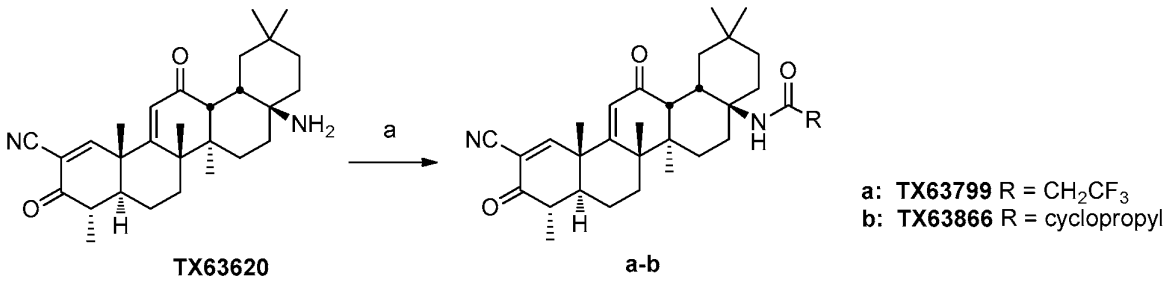
Reagents and conditions: a) RCl, TEA, DCM, 0 °C or rt, 1-2 hr.

Scheme 59



Reagents and conditions: a) HCOOAc, TEA, DCM, 0 °C, 1 hr, 68%.

Scheme 60



TX63620 **a-b**

Reagents and conditions: a) T3P, TEA, DCM, RCOOH, rt, 2 h, **TX63799**: 20%, **TX63866**: 42%.

Synthesis and Characterization of Compounds and Intermediates

Compound 2: Compound **1** (40 g, 83.0 mmol), NH_2OH-HCl (13.33 g, 191.8 mmol), NaOAc (15.60 g, 190.2 mmol), CH_2Cl_2 (400 mL) and MeOH (400 mL) were mixed in a 2 L flask. The heterogeneous reaction mixture was stirred at 70 °C (oil bath temperature) for 1.5 hrs, and then, was cooled to room temperature. The solvent was removed on a rotary evaporator. The residue was dissolved in CH_2Cl_2, and was washed with water. The organic extract was dried with $MgSO_4$, and concentrated to give the crude product as a white foam solid. The crude product was dissolved in CH_2Cl_2, and the solution was filtered through a 2-inch pad of silica gel eluting with CH_2Cl_2/EtOAc (1:1, 1 L). The filtrate and washes were combined, and concentrated to give oxime **2** (43.44 g) as a white foam solid: m/z 498.3 (M+1).

Compound 3: Compound **2** (43.44 g, 87.22 mmol) obtained above was dissolved in AcOH (217 mL) and Ac_2O (217 mL), and the reaction was stirred at room temperature for 2 h. $PhI(OAc)_2$ (42.13 g, 131 mmol) and $Pd(OAc)_2$ (0.98 g, 4.37 mmol, 0.05 eq.) were added. The flask was sealed, and the mixture was heated in a 60 °C oil bath for 24 hrs. After cooling to room temperature, toluene was added, and most of the AcOH was removed by azeotropic evaporation with toluene on a rotary evaporator. The red oil obtained was slowly poured into a suspension of $NaHCO_3$ (150 g) in water (500 mL). After the mixture was stirred at room temperature for 15 min, it was extracted with CH_2Cl_2. The combined organic extracts was washed with aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give product **3** (23.56 g, 47.5% yield from **1**) as a yellow foam solid. Compound **3** is a 4.4:1 mixture of C4-diastereomers: m/z 598.4 (M+1), 538.4 (M-OAc).

Compounds 4 and 5: K_2CO_3 (27.38 g, 197.1 mmol) was added to a solution of compound **3** (23.56 g, 39.4 mmol) in MeOH (390 mL) at 0 °C. After the reaction was stirred at room temperature for 1 hr, the solvent was removed on a rotary evaporator. The residue was treated with CH_2Cl_2 and 12 N HCl (33 mL, 396 mmol). After the mixture was stirred for 5 min, it was transferred to a separatory funnel, which was extracted with CH_2Cl_2. The combined organic extracts was washed with water, dried with $MgSO_4$, and concentrated. The crude product was purified by column chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to

give product **4** (15.25 g, 75% yield) as a light yellow solid: m/z 514.1 (M+1). From the column, also get product **5** (2.20 g, 11% yield) as a yellow foam: m/z 514.1 (M+1).

Compound 6: Compound **4** (17.25 g, 33.6 mmol), $NaHSO_3$ (12.21 g, 117.4 mmol), EtOH (135 mL) and water (68 mL) were mixed, and heated in an 80 °C oil bath for 3 hrs. Additional amount of $NaHSO_3$ (3.49 g, 33.6 mmol) was added, and the reaction was heated for another 1 hr. After EtOH was removed on a rotary evaporator, the residue was extracted with EtOAc. The combined organic extracts was washed with water, dried with $MgSO_4$, and concentrated to give the crude product, which was dissolved in CH_2Cl_2, and was filtered through a 1-inch pad of silica gel, eluting with CH_2Cl_2/EtOAc (1:1, 800 mL). The filtrate was concentrated to give Compound **6** (14.20 g, 85% yield) as a white solid: m/z 499.3 (M+1).

Compound 7: Compound **6** (14.20 g, 28.5 mmol) was dissolved in xylene (600 mL), and was heated at reflux for 28 hrs. After the reaction was cooled to room temperature, the solvent was removed on a rotary evaporator to give the crude product **7** as a yellow solid. Crude **7** was dissolved in CH_2Cl_2 (50 mL) and EtOH (50 mL), and the solution was evaporated on a rotary evaporator until most of CH_2Cl_2 was removed. Additional amount of EtOH (25 mL) was added. The heterogeneous mixture was heated at reflux for 10 min, after which, it was allowed to stand at room temperature for 1 hr. The precipitate was collected by filtration, washed with EtOH, and dried under vacuum for 16 hrs to give compound **7** (11.40 g, 85% yield) as a white solid. Compound **7** is a 15:1 mixture of the two C4-epimers: m/z 469.3 (M+1).

Compound 8: NaOMe (29.40 mL, 128.6 mmol) was added to a solution of compound **7** (4.02 g, 8.57 mmol) in THF (8.6 mL) at 0 °C. After the reaction was stirred for 10 min, it was treated with HCO_2Et (20.70 mL, 257.4 mmol), and was stirred at ambient temperature for 2.5 hrs. After the mixture was cooled to 0 °C, MTBE (90 mL) and 12 N HCl (11 mL) were added. The mixture was stirred for 2 min, and was partitioned between water and EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated to give compound **8** as a pink foam solid: m/z 497.3 (M+1).

Compound 9: Compound **8** obtained above, NH_2OH-HCl (900 mg, 12.9 mmol), EtOH (86 mL) and water (8.6 mL) were mixed and heated at 55 °C for 3 hrs. After EtOH was removed on a rotary evaporator, the residue was extracted with CH_2Cl_2. The combined organic extracts was washed with water, dried with $MgSO_4$,

and concentrated. The crude product was triturated with EtOH (20 mL) at reflux for 20 min, and the mixture was allowed to stand at room temperature for 2 hrs. The precipitate was collected by filtration, washed with EtOH, and dried under vacuum for 16 hrs to give compound **9** (2.40 g, 57% yield from **7**) as a white solid. The mother liquor was concentrated, and the residue was purified by column chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give a second crop of product **9** (820 mg, 19% yield from **7**) as a white solid. Compound **9**: m/z 494.3 (M+1).

Compound 10 (TX63778): NaOMe (2.05 mL, 8.96 mmol) was added to a suspension of compound **9** (3.195 g, 6.47 mmol) in MeOH (65 mL) at room temperature. After the reaction was heated at 55 °C for 2 hrs, it was cooled to room temperature. MTBE was added, and the mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl, and water. The organic extract was dried with $MgSO_4$, and concentrated to give compound **10** as an off-white solid: m/z 494.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (s, 1H), 3.72 (dd, 1H, J = 5.7, 13.6 Hz), 3.69 (s, 3H), 3.03 (m, 1H), 2.91 (d, 1H, J = 4.5 Hz), 2.68 (dd, 1H, J = 5.6, 13.1 Hz), 2.43 (m, 1H), 2.01 (dd, 1H, J = 13.2, 13.4 Hz), 1.41 (s, 3H), 1.31 (s, 3H), 1.13 (d, 3H, J = 6.4 Hz), 1.10-1.95 (m, 15H), 1.00 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound TX63435: A solution of 1,3-dibromo-5,5-dimethylhydantoin (939 mg, 3.28 mmol) in DMF (10 mL) was added to a solution of compound **10** obtained above in DMF (25 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 hr, pyridine (1.68 mL, 20.8 mmol) was added. The reaction was heated at 55 °C for 3.5 hrs, and was cooled to room temperature. The mixture was diluted with EtOAc, and was transferred to a separatory funnel, which was washed with 1 N aq. HCl, aq. Na_2SO_3 solution, and water. The organic extract was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give **TX63435** (2.727 g, 85% yield from **9**) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.026 (s, 1H), 3.71 (s, 3H), 3.05 (m, 1H), 2.96 (d, 1H, J = 4.5 Hz), 2.48 (m, 1H), 1.45 (s, 3H), 1.33 (s, 3H), 1.26 (d, 3H, J = 6.5 Hz), 1.20-1.95 (m, 15H), 1.02 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); m/z 492.3 (M+1).

Compound TX63520: LiI (14.85 g, 110.8 mmol) was added to a solution of compound **10** (2.727 g, 5.54 mmol) in DMF (40 mL) at room temperature. After the reaction was heated at 150 °C with N_2 bubbled through for 4 hrs, it was cooled, and

was diluted with EtOAc. The mixture was washed with 1 N aq. HCl, and water. The aq. washes were extracted again with EtOAc. The combined EtOAc extracts was washed with aq. Na_2SO_3, and water, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 10% MeOH on CH_2Cl_2) to give **TX63520** (1.700 g, 64% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 3.01-3.05 (m, 2H), 2.47 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.25 (d, 3H, J = 6.8 Hz), 1.18-1.97 (m, 15H), 1.02 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H); m/z 478.3 (M+1).

Compound TX63521: Oxalyl chloride (0.35 mL, 4.13 mmol) and DMF (11 μL, 0.14 mmol) were added sequentially to a solution of **TX63520** (660 mg, 1.38 mmol) in CH_2Cl_2 (28 mL) at 0 °C. After the reaction was stirred at ambient temperature for 2 hrs, it was concentrated on a rotary evaporator. The residue was co-evaporated with toluene (3 × 10 mL) to remove residual oxalyl chloride. Compound **11** was obtained as a light yellow foam solid.

The acid chloride **11** was dissolved in CH_2Cl_2 (14 mL), and was cooled to 0 °C. $EtNH_2$ (2.0 M solution in THF, 2.07 mL, 4.14 mmol) was added. After the reaction was stirred at 0 °C for 30 min, it was transferred to a separatory funnel, which was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give **TX63521** (704 mg, 100% yield) as a white solid, which was contaminated with a small amount of impurities. The **TX63521** obtained was further purified by triturated with EtOH (5 mL) at 55 °C for 10 min. After the mixture was allowed to stand at room temperature for 1 hr, the white precipitate was collected by filtration, washed with EtOH, and dried under vacuum for 16 hrs to give **TX63521** (504 mg) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.01 (s, 1H), 5.74 (t, 1H, J = 5.4 Hz), 3.30 (m, 2H), 3.06 (d, 1H, J = 4.2 Hz), 2.84 (m, 1H), 2.46 (m, 1H), 1.43 (s, 3H), 1.32 (s, 3H), 1.24 (d, 3H, J = 6.6 Hz), 1.14-1.96 (m, 15H), 1.12 (t, 3H, J = 7.2 Hz), 1.01 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H); m/z 505.3 (M+1).

Compound 12: LiI (67.89 g, 506.6 mmol) was added to a solution of compound **7** (11.88 g, 25.3 mmol) in DMF (180 mL) at room temperature. The mixture was heated at 150 °C with N_2 bubbled through for 7.5 h. After the reaction was cooled, it was diluted with EtOAc, and was washed with 1 N aq. HCl, and water. The aqueous washes were extracted again with EtOAc. The combined EtOAc

extracts was washed with aq. Na_2SO_3, and water, dried over Na_2SO_4, and concentrated on a rotary evaporator to approximately 40 mL. The yellow heterogeneous mixture was refluxed for 20 min, after which, it was allowed to stand at room temperature for 5 h. The precipitate was collected by filtration, washed with EtOAc/hexane (1:1), and dried under vacuum for 16 h to give compound **12** (9.15 g, 79% yield) as a white solid. The mother liquor was concentrated, and the residue was purified by column chromatography (silica gel, eluting with 0% to 35% EtOAc in CH_2Cl_2) to give a second crop of compound **12** (1.65 g, 14% yield) as a white solid. Compound **12**: m/z 455.3 (M+1).

Compound 13: NaOMe (87 mL, 380.5 mmol) was added to a suspension of compound **12** (11.54 g, 25.4 mmol) in HCO_2Et (61 mL, 758.4 mmol) at 0 °C. After the reaction was stirred at ambient temperature for 1 h, it was cooled to 0 °C. MTBE (250 mL) and 6 N aq. HCl (67.6 mL, 405.6 mmol) were added sequentially. After stirring for 5 min, the mixture was transferred to a separatory funnel, and was extracted with EtOAc. The combined organic extracts was washed with 1 N aq. HCl, and water, dried with Na_2SO_4, and concentrated.

The residue was mixed with NH_2OH-HCl (2.66 g, 38.3 mmol), EtOH (250 mL) and water (25 mL), and was heated at 55 °C for 3 h. After EtOH was removed on a rotary evaporator, the residue was extracted with CH_2Cl_2. The combined organic extracts was washed with water, dried with Na_2SO_4, and concentrated to give the crude product as a pink solid. Crude **7** was triturated with EtOAc (25 mL) at reflux for 10 min, and the mixture was allowed to stand at room temperature for 2 h. The precipitate was collected by filtration, washed with EtOAc/hexane (1:1), and dried under vacuum for 16 h to give compound **13** (9.70 g, 80% yield) as a light pink solid: m/z 480.3 (M+1).

Compound 14: Oxalyl chloride (3.31 mL, 39.0 mmol) and DMF (0.10 mL, 1.29 mmol) were added sequentially to a solution of compound **13** (6.25 g, 13.0 mmol) in CH_2Cl_2 (130 mL) at 0 °C. After the reaction was stirred at ambient temperature for 2 h, it was concentrated on a rotary evaporator. The residue was co-evaporated with toluene (3 × 50 mL) to remove residual oxalyl chloride. Crude acid chloride was obtained as a light brown solid.

The acid chloride was dissolved in CH_2Cl_2 (130 mL), and was cooled to 0 °C. $EtNH_2$ (2.0 M solution in THF, 19.5 mL, 39.0 mmol) was added, and the reaction was stirred at 0 °C for 40 min. The mixture was transferred to a separatory funnel, which

was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The crude product was dissolved in minimal amount of CH_2Cl_2, and EtOH (10 mL) was added. After the mixture was heated at reflux for 10 min to evaporate the CH_2Cl_2, it was allowed to stand at 4 °C for 16 h. The precipitate was collected by filtration, washed with EtOH, and dried under vacuum for 16 h to give compound **14** (5.66 g, 86% yield) as a white solid: m/z 507.3 (M+1).

Compound 15: NaOMe (5.11 mL, 22.3 mmol) was added to a solution of compound **14** (5.66 g, 11.2 mmol) in MeOH (112 mL) at room temperature. After the reaction was heated at 55 °C for 2 h, it was cooled to room temperature. MTBE (200 mL) was added, and the mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl, and water. The aqueous washes were extracted again with EtOAc. The combined organic extracts was dried with Na_2SO_4, and concentrated to give crude product **15** as a white solid. Crude **15** was triturated with EtOAc (20 mL) at reflux for 5 min, and was allowed to stand at room temperature for 2 h. The precipitate was collected by filtration, washed with EtOAc, and dried under vacuum for 16 h to give compound **15** (5.22 g, 92% yield) as a white solid. Compound **15** is a 1.75:1 mixture of A-ring enol and ketone isomers: m/z 507.3 (M+1).

Compounds TX63521 and TX63597: A solution of 1,3-dibromo-5,5-dimethylhydantoin (1.472 g, 5.15 mmol) in DMF (26 mL) was added to a solution of compound **15** (5.218 g, 10.3 mmol) in DMF (25 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (2.50 mL, 31.0 mmol) was added, and the mixture was heated at 55 °C for 3 h. After cooling to room temperature, the reaction was diluted with EtOAc (300 mL), and was transferred to a separatory funnel, which was washed with 1 N aq. HCl, aq. Na_2SO_3, and water. The organic extract was dried with Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel, eluting with 1:1 EtOAc:CH_2Cl_2 (400 mL). The filtrate was concentrated to give the crude product, which was triturated from CH_2Cl_2/EtOH to give **TX63521** (4.37 g, 84% yield) as a white solid: m/z 505.3 (M+1). The mother liquor was concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in (10:1 hexanes:CH_2Cl_2)) to give a second crop of **TX63521** (0.67 g, 12% yield) as a white solid. From the mother liquor, compound **TX63597** (12 mg, 2% yield) was also obtained as a white solid: m/z = 503.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 5.95 (s, 1H), 5.76 (t, 1H, J = 5.3 Hz), 3.33 (m, 2H), 3.13 (d, 1H, J = 4.5 Hz), 2.94 (m, 1H), 2.86 (m, 1H), 2.60 (m, 1H), 2.01 (s, 3H), 1.95 (m, 1H), 1.65 (s, 3H),

1.50 (s, 3H), 1.15-1.85 (m, 11H), 1.15 (t, 3H, J = 7.2 Hz), 1.00 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H).

Compound TX63522: Imidazole (75 mg, 1.10 mmol) was added to a solution of compound **11** (184 mg, 0.37 mmol)) in benzene (3.7 mL) at 10 °C. After the reaction was stirred for 40 min, additional amount of imidazole (25 mg, 0.37 mmol) was added. After the reaction was continued to stir for another 30 min, it was diluted with EtOAc. The mixture was transferred to a separatory funnel, which was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in CH_2Cl_2) to give **TX63522** (150 mg, 77% yield) as a white foam solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.00 (s, 1H), 7.61 (s, 1H), 7.08 (s, 1H), 6.02 (s, 1H), 3.19-3.22 (m, 2H), 2.45 (m, 1H), 2.23 (m, 1H), 1.43 (s, 3H), 1.27 (s, 3H), 1.23 (d, 3H, J = 7.2 Hz), 1.20-2.04 (m, 14H), 1.04 (s, 6H), 0.95 (s, 3H); m/z 528.3 (M+1).

Compound TX63523: $CF_3CH_2NH_2$ (359 mg, 3.62 mmol) was added to a solution of compound **11** (600 mg, 1.21 mmol) in CH_2Cl_2 (12 mL) at room temperature. After the reaction was stirred for 1 hr, it was diluted with EtOAc, transferred to a separatory funnel, which was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was triturated with EtOH at 55 °C for 10 min. After the mixture was allowed to stand at room temperature for 1 hr, the white precipitate was collected by filtration, washed with EtOH, and dried under vacuum for 16 hrs to give **TX63523** (320 mg, 47% yield) as a white solid. The mother liquor was concentrated, and the residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give a second crop of **TX63523** (235 mg, 35% yield) as a white solid. Compound **TX63523**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.02 (s, 1H), 5.99 (t, 1H, J = 6.6 Hz), 3.88-4.05 (m, 2H), 3.05 (d, 1H, J = 4.8 Hz), 2.92 (m, 1H), 2.46 (m, 1H), 2.03 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.24 (d, 3H, J = 6.0 Hz), 1.18-1.89 (m, 14H), 1.02 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H); m/z 559.3 (M+1).

Compound 16: Oxalyl chloride (2.10 mL, 24.8 mmol) and catalytic amount of DMF were added sequentially to a solution of compound **13** (3.99 g, 8.32 mmol) in CH_2Cl_2 (83 mL) at 0 °C. After the reaction was stirred at ambient temperature for 2 h, it was concentrated on a rotary evaporator. The residue was co-evaporated with

toluene (3 × 30 mL) to remove residual oxalyl chloride. Crude acid chloride was obtained as a light brown solid.

The acid chloride was dissolved in CH_2Cl_2 (83 mL), and was cooled to 0 °C. $CF_3CH_2NH_2$ (1.90 mL, 24.9 mmol) was added, and the reaction was stirred at 0 °C for 90 min. The mixture was transferred to a separatory funnel, which was washed with water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexane) to give compound **16** (3.95 g, 85% yield) as a white solid: m/z 561.3 (M+1).

Compound 17: NaOMe (2.30 mL, 10.1 mmol) was added to a solution of compound **16** (3.95 g, 7.04 mmol) in MeOH (70 mL) at room temperature. After the reaction was heated at 55 °C for 2 h, it was cooled to room temperature. MTBE (200 mL) was added, and the mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl, and water. The organic extract was dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 60% EtOAc in hexane) to give compound **17** (3.18 g, 81% yield) as a white solid: m/z 561.3 (M+1).

Compound TX63523: A solution of 1,3-dibromo-5,5-dimethylhydantoin (1.22 g, 4.27 mmol) in DMF (15 mL) was added to a solution of compound **17** (4.80 g, 8.55 mmol) in DMF (20 mL) at 0 °C via syringe. The syringe was rinsed with DMF (8 mL), and was added to the reaction mixture. After the reaction was stirred at 0 °C for 1 h, pyridine (2.07 mL, 25.7 mmol) was added, and the mixture was heated at 55 °C for 3 h. After cooling to room temperature, the reaction was diluted with EtOAc, and was transferred to a separatory funnel, which was washed with 1 N aq. HCl, aq. Na_2SO_3, and water. The organic extract was dried with Na_2SO_4 and concentrated to give crude compound **TX63523** (4.70 g, 98% yield) as a light yellow solid. Crude compound **TX63523** was dissolved in CH_2Cl_2 (30 mL) and EtOH (15 mL). The solution was evaporated on a rotary evaporator until most of CH_2Cl_2 was removed. The heterogeneous mixture was heated at reflux for 20 min, and was allowed to stand at room temperature for 1 h. The precipitate was collected by filtration, washed with EtOH, and dried under vacuum for 16 h to give compound **TX63523** (4.04 g, 86% yield) as a white solid: m/z 559.2 (M+1).

Compound 18: $LiAlH_4$ (2.0 M in THF, 0.30 mL, 0.60 mmol) was added to a solution of compound **9** (100 mg, 0.20 mmol) in THF (4.0 mL) at 0 °C. After the reaction was stirred at 0 °C for 4 hrs, additional amount of $LiAlH_4$ (2.0 M in THF,

0.10 mL, 0.20 mmol) was added. After the reaction was stirred for another 2 hrs, it was quenched by the addition of EtOH. EtOAc was added, and the mixture was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 80% EtOAc in hexane) to give compound **18** (56 mg, 59% yield) as a white foam solid: m/z 468.3 (M+1).

Compound 19: NBS (30 mg, 0.17 mmol) was added to a solution of compound **18** (53 mg, 0.11 mmol) in DME (1 mL) and water (0.1 mL) at room temperature. After the reaction was stirred at room temperature while shielded from light for 25 min, aq. Na_2SO_3 was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 60% EtOAc in hexane) to give compound **19** (50 mg, 94% yield) as a white foam solid: m/z 466.3 (M+1).

Compound 20: NaOMe (37 μL, 0.16 mmol) was added to a solution of compound **19** (50 mg, 0.11 mmol) in MeOH (1.1 mL) at room temperature. After the reaction was heated at 55 °C for 1 hr, it was cooled to room temperature. MTBE was added, and the mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl, and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 80% EtOAc in hexane) to give compound **20** (47 mg, 94% yield) as a white foam solid: m/z 466.3 (M+1).

Compound TX63545: A solution of 1,3-dibromo-5,5-dimethylhydantoin (14 mg, 0.049 mmol) in DMF (0.2 mL) was added to a solution of compound **20** (46 mg, 0.099 mmol) in DMF (0.3 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 hr, pyridine (24 μL, 0.30 mmol) was added. The reaction was heated at 55 °C for 3 hrs, and was cooled to room temperature. The mixture was diluted with EtOAc, and was washed with 1 N aq. HCl, aq. Na_2SO_3 solution, and water. The organic extract was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 80% EtOAc in hexanes) to give **TX63545** (37 mg, 80% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.05 (s, 1H), 3.63 (dd, 1H, J = 6.5, 10.8 Hz), 3.54 (dd, 1H, J = 4.6, 10.8 Hz), 2.97 (d, 1H, J = 4.6 Hz), 2.50 (m, 1H), 2.38 (m, 1H), 1.47 (s, 6H), 1.27 (d, 3H, J = 6.7 Hz), 1.10-1.93 (m, 16H), 1.04 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H); m/z 464.3 (M+1).

Compound TX63546: Ac_2O (11 μL, 0.12 mmol) was added to a solution of compound **TX63545** (10.7 mg, 0.023 mmol) and pyridine (19 μL, 0.23 mmol) in CH_2Cl_2 (0.23 mL) at room temperature. After the reaction was stirred at room temperature for 3 hrs, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with 1 N aq. HCl, and water, dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 80% EtOAc in hexanes) to give **TX63546** (9 mg, 77% yield) as a white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 4.11 (d, 1H, J = 11.2 Hz), 4.01 (d, 1H, J = 11.2 Hz), 3.00 (d, 1H, J = 4.6 Hz), 2.48 (m, 1H), 2.38 (m, 1H), 2.09 (s, 3H), 1.51 (s, 3H), 1.46 (s, 3H), 1.25 (d, 3H, J = 6.8 Hz), 1.10-1.91 (m, 15H), 1.02 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H); m/z 506.3 (M+1).

Compound TX63555 and **TX63556**: **TX63520** (65 mg, 0.14 mmol), IPh(OH)(OTs) (64 mg, 0.16 mmol) and CH_2Cl_2 (2.7 mL) were mixed and heated at reflux for 1 hr. After cooling to room temperature, the mixture was purified by column chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give **TX63555** (34 mg, 53% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.25 (s, 1H), 2.98 (m, 1H), 2.52 (m, 1H), 2.11 (m, 1H), 1.53 (s, 3H), 1.53 (s, 3H), 1.27 (d, 3H, J = 6.8 Hz), 1.22-1.93 (m, 14H), 1.02 (s, 3H), 0.97 (s, 6H); m/z 476.2 (M+1).

From the column, **TX63556** (24 mg, 37%) was also obtained as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 5.92 (s, 1H), 2.97 (t, 1H, J = 8.4 Hz), 2.49 (m, 1H), 2.37 (m, 1H), 1.56 (s, 3H), 1.47 (s, 3H), 1.22-2.02 (m, 14H), 1.20 (d, 3H, J = 6.8 Hz), 1.17 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H); m/z 476.3 (M+1).

Compound TX63557: NH_3 (2.0 M in MeOH, 0.50 mL, 1.00 mmol) was added to a solution of compound **11** (104 mg, 0.21 mmol) in THF (2.1 mL) at 0 °C. After the reaction was stirred at 0 °C for 30 min, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give **TX63557** (95 mg, 95% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.04 (s, 1H), 5.74 (bs, 1H), 5.31 (bs, 1H), 3.15 (d, 1H, J = 4.5 Hz), 2.88 (m, 1H), 2.48 (m, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 1.27 (d, 3H, J = 6.7 Hz), 1.19-2.04 (m, 15H), 1.04 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H); m/z 477.3 (M+1).

Compound TX63558: Et_3N (51 μL, 0.37 mmol) and TFAA (30 μL, 0.22 mmol) were added sequentially to a solution of **TX63557** (70 mg, 0.15 mmol) in CH_2Cl_2 at 0 °C. After the reaction was stirred at 0 °C for 15 min, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with CH_2Cl_2. The combined organic extracts was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give **TX63558** (51 mg, 83% yield) as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.07 (s, 1H), 3.29 (d, 1H, J = 4.7 Hz), 2.80 (m, 1H), 2.50 (m, 1H), 2.21 (m, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.27 (d, 3H, J = 6.9 Hz), 1.18-2.08 (m, 14H), 1.03 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H); m/z 459.2 (M+1).

Compound **21**: A mixture of Compound **11** (176 mg, 0.35 mmol) in ether (3.0 mL) was cooled to 0 °C. Et_3N (99 μL, 0.71 mmol) and $AcNHNH_2$ (40 mg, 0.53 mmol) in CH_2Cl_2 (8 mL) were added sequentially. The reaction was stirred at room temperature for 30 min, after which, additional amount of $AcNHNH_2$ (40 mg, 0.53 mmol) was added. After stirring for another 2 h, the mixture was diluted with EtOAc, and was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **21** (130 mg, 68% yield) as a white foam solid: m/z 534.2 (M+1).

Compound TX63616: A mixture of compound **21** (28 mg, 0.052 mmol), $TsOH{\cdot}H_2O$ (5 mg, 0.026 mmol) and toluene (2 mL) was heated at reflux with a dean-stark apparatus for 2 hrs. The mixture was transferred to a separatory funnel, which was washed with aq. $NaHCO_3$ and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 65% EtOAc in hexanes) to give compound **TX63616** (20 mg, 74% yield) as a white foam solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.02 (s, 1H), 3.15 (m, 1H), 2.97 (d, 1H, J = 4.6 Hz), 2.54 (s, 3H), 2.47 (m, 1H), 2.19 (m, 1H), 1.42 (s, 3H), 1.26 (d, 3H, J = 6.7 Hz), 1.20-2.03 (m, 14H), 1.20 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H); m/z 516.2 (M+1).

Compound 22: Et_3N (0.44 mL, 3.16 mmol) and DPPA (103 μL, 0.48 mmol) were added sequentially to a solution of compound **TX63520** (76 mg, 0.16 mmol) in toluene (1.6 mL) at 0 °C. After the reaction was stirred at room temperature for 4 h,

the solvent was removed by evaporation. The residue was purified by column chromatography (silica gel, 0 to 30% EtOAc in hexanes) to give azide **22** (63 mg, 79%) as white foam solid: m/z 503.2 (M+1).

Compound TX63618: A solution of compound **22** (63 mg, 0.13 mmol) in toluene (5 mL) was heated at 80 °C for 3 h. The solvent was removed, and the residue was purified by column chromatography (silica gel, 0 to 3% EtOAc in CH_2Cl_2) to give compound **TX63618** (54 mg, 91%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.06 (s, 1H), 3.30 (d, 1H, *J* = 4.7 Hz), 2.54 (m, 1H), 2.50 (m, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 1.28 (d, 3H, *J* = 6.7 Hz), 1.15-2.14 (m, 15H), 1.04 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H); m/z 475.2 (M+1).

Compound TX63620: 12 N aq. HCl (0.5 mL, 6.00 mmol) was added to a solution of compound **TX63618** (49 mg, 0.10 mmol) in MeCN (0.5 mL) at 0 °C, and the reaction was stirred at room temperature for 1 hr. CH_2Cl_2 and 10% aq. NaOH (2.4 mL, 6.00 mmol) were added. The mixture was transferred to a separatory funnel, which was washed with aq. $NaHCO_3$ and water. The organic extract was dried with $MgSO_4$, and concentrated to give compound **TX63620** (45 mg, 97% yield) as an off-white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.04 (s, 1H), 3.65 (d, 1H, *J* = 4.4 Hz), 2.50 (m, 1H), 2.23 (m, 1H), 1.52 (s, 3H), 1.48 (s, 3H), 1.28 (d, 3H, *J* = 6.7 Hz), 1.00 (s, 6H), 0.98-2.14 (m, 15 H), 0.90 (s, 3H); m/z 449.2 (M+1).

Compound TX63621: Et_3N (59 μL, 0.42 mmol) and $MeSO_2Cl$ (5 μL, 0.064 mmol) were added sequentially to a solution of compound **TX63620** (19 mg, 0.042 mmol) in CH_2Cl_2 (0.42 mL) at 0 °C. After the reaction was stirred at 0°C for 1 hr, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 70% EtOAc in hexanes) to give compound **TX63621** (8 mg, 36%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.15 (s, 1H), 4.27 (s, 1H), 3.22 (d, 1H, *J* = 4.4 Hz), 3.11 (s, 3H), 2.54 (m, 1H), 2.50 (m, 1H), 1.51 (s, 3H), 1.46 (s, 3H), 1.27 (d, 3H, *J* = 6.7 Hz), 1.05 (s, 3H), 1.03 (s, 3H), 0.95-2.18 (m, 15H), 0.93 (s, 3H); m/z 432.2 (M-$MeSO_2$).

Compound TX63622: Et_3N (18 μL, 0.13 mmol) and AcCl (6 μL, 0.085 mmol) were added sequentially to a solution of compound **TX63620** (19 mg, 0.042 mmol) in CH_2Cl_2 (0.42 mL) at 0 °C. After the reaction was stirred at 0°C for 30 min, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which

was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 70% EtOAc in hexanes) to give compound **TX63622** (20 mg, 96%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.06 (s, 1H), 5.00 (s, 1H), 3.10 (d, 1H, J = 4.7 Hz), 2.60 (m, 1H), 2.49 (m, 1H), 2.29 (m, 1H), 1.97 (s, 3H), 1.47 (s, 3H), 1.45 (s, 3H), 1.28 (d, 3H, J = 6.5 Hz), 1.15-2.15 (m, 14H), 1.04 (s, 6H), 0.91 (s, 3H); m/z 491.2 (M+1).

Compound TX63682: TX63620: (77 mg, 0.17 mmol), $CH_3CF_2CO_2H$ (22.7 mg, 0.21 mmol) were dissolved in CH_2Cl_2 (2 mL). DCC (53 mg, 0.26 mmol) and DMAP (8.4 mg, 0.069 mmol) were added. The reaction was stirred at room temperature for 16 h. The reaction mixture was filtered. The filtrate was purified by column chromatography (silica gel, eluting with 0-40% EtOAc in hexanes) to give **TX63682** (75 mg, 81% yield) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.05 (s, 1H), 5.92 (s, 1H), 3.02 (d, 1H, J = 4.2 Hz), 2.79 (m, 1H), 2.48 (m, 1H), 1.78 (t, 3H, J = 19.3 Hz), 1.46 (s, 3H), 1.42 (s, 3H), 1.27 (d, 3H, J = 6.5 Hz), 1.17-2.35 (m, 15 H), 1.06 (s, 3H), 1.04 (s, 3H), 0.91 (s, 3H); m/z = 541.3 (M+1).

Compound TX63984: 10% Pd/C (30 mg) was added to a solution of **TX63682** (100 mg, 0.18 mmol) in EtOAc (2 mL). After the mixture was hydrogenated (balloon) for 2 h at room temperature, the catalyst was removed by filtered through a pad of silica gel. The filtrate was concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-30% EtOAc in hexanes) to give **TX63984** (85 mg, 85% yield) as a white solid: 3:1 mixtire of ketone:enol isomers, m/z = 543.3 (M+1); Ketone isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (bs, 1H), 5.84 (s, 1H), 3.72 (dd, 1H, J = 5.8, 13.6 Hz), 2.97 (d, 1H, J = 4.6 Hz), 2.74 (m, 1H), 2.67 (dd, 1H, J = 5.9, 13.2 Hz), 2.46 (m, 1H), 1.76 (t, 3H, J = 19.3 Hz), 1.41 (s, 3H), 1.39 (s, 3H), 1.12 (d, 3H, J = 6.6 Hz), 1.10-2.15 (m, 16H), 1.04 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H).

Compound 24: $TMSCHN_2$ (2.0 M solution in ether, 10.60 mL, 21.20 mmol) was added to a mixture of compound **23** (10.00 g, 21.16 mmol) in toluene (150 mL) and MeOH (50 mL) at 0 °C. After the heterogeneous reaction mixture was stirred at 0-10 °C for 1 h, additional amount of $TMSCHN_2$ (2.0 M solution in ether, 5.30 mL, 10.60 mmol) was added. After another 1 h, the reaction was quenched by AcOH. EtOAc was added. The mixture was transferred to a seperatory funnel, which was washed with aq. $NaHCO_3$ and water. The organic extract was separated, dried with

$MgSO_4$, filtered, and concentrated. The residue was recrystallized with EtOH to give compound **24** (5.20 g, 51% yield) as a white solid. The mother liquor was concentrated, and the residue was purified by column chromatography (silica gel, 0 to 70% EtOAc in hexanes) to give a second crop of compound **24** (4.60 g, 45% yield) as a white solid: m/z 487.3 (M+1), 451.4.

Compound 25: DMSO (6.75 mL, 95.03 mmol) was added drop wise to a solution of oxalyl chloride (4.02 mL, 47.51 mmol) in CH_2Cl_2 (50 mL) at -78 °C. After stirring for 30 min, compound **24** (4.63 g, 9.51 mmol) in CH_2Cl_2 (45 mL) was added at -78 °C. After stirring for another 1 h, the reaction was treated with Et_3N (26.5 mL, 190.2 mmol), and continued stirring for 30 min at ambient temperature. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with aq. $NaHCO_3$ and water. The organic extract was separated, dried with $MgSO_4$, and concentrated to give compound **25**: m/z = 483.3 (M+1). Compound **25** was used in the next step without further purification.

Compound 26: NaOMe (3.30 mL, 14.43 mmol) was added to a mixture of compound **25** in MeOH (95 mL) at room temperature. After stirring for 30 min, the reaction was cooled to 0 °C. MTBE and 6 N aq. HCl (2.50 mL, 15.00 mmol) were added. The mixture was transferred to a separatory funnel, which was washed with water. The aqueous wash was extracted with EtOAc. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL) and EtOH (30 mL). The solution was evaporated on a rotary evaporator to remove CH_2Cl_2. After the white slurry was allowed to stand at room temperature for 60 h, the precipitate was collected by filtration, and was washed with EtOH to give compound **26** (3.29 g, 76% yield from **24**) as a white solid: m/z = 455.3 (M+1).

Compound 27: NaOMe (24.80 mL, 108.5 mmol) was added to a mixture of compound **26** (3.29 g, 7.24 mmol) and HCO_2Et (17.4 mL, 216.3 mmol) at 0 °C. After the reaction was stirred at room temperature for 1 h, THF (5 mL) was added. After another 2 h, THF (5 mL) was added again, and the reaction was stirred for another 3 h. The reaction was cooled to 0 °C. MTBE and 6 N HCl (19 mL, 114 mmol) were added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was mixed with NH_2OH-HCl (760 mg, 10.94 mmol), EtOH (162 mL) and water (8 mL), and the reaction was stirred at 55 °C for 16 h.

After EtOH was removed on a rotary evaporator, the residue was extracted with EtOAc. The combined organic extracts were washed with water, dried with $MgSO_4$, and concentrated. The crude product was triturated with MeOH (10 mL) at reflux for 10 min, and the mixture was allowed to stand at room temperature for 1 h. The precipitate was collected by filtration, washed with MeOH, and dried under vacuum for 16 h to give compound **27** (2.87 g, 83% yield) as an off-white solid: m/z 480.3 (M+1).

Compound 28: AcO_2H (39% in AcOH, 410 μL, 3.15 mmol) was added to a solution of compound **27** (1.00 g, 2.08 mmol) in AcOH (10.4 mL) at room temperature. After heated at 55 °C for 18 h, the reaction was cooled to room temperature, and was treated with aq. Na_2SO_3. The product was extracted with CH_2Cl_2. The combined organic extracts were washed with aq. Na_2SO_3, and aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-25% EtOAc in hexanes) to give compound **28** (825 mg, 80% yield) as a white solid: m/z = 496.3 (M+1).

Compound 29: NaOMe (570 μL, 2.49 mmol) was added to a mixture of compound **28** (823 mg, 1.67 mmol) and MeOH (17 mL) at room temperature. After the reaction was heated at 55 °C for 1 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated to give compound **29** as a white solid: m/z = 496.3 (M+1). Compound **29** was used in the next step without further purification.

Compound TX63749: A solution of DBDMH (236 mg, 0.83 mmol) in DMF (4 mL) was added to a solution of cyanoketone **29** in DMF (4.25 mL) at 0 °C. After stirring at 0 °C for 1 h, pyridine (0.40 mL, 4.96 mmol) was added. After the reaction was heated at 55 °C for 3 h, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was triturated with CH_2Cl_2/EtOH to give compound **TX63749** (744 mg, 90% yield from **28**) as a white solid: m/z 494.3 (M+1), 434.3 (M-CO_2Me); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 3.68 (s, 3H), 2.81 (m, 1H), 2.68 (d, 1H, J = 3.8 Hz), 2.48 (dd, 1H, J = 4.4, 16.3 Hz), 2.33-2.46 (m, 2H), 1.21 (d, 3H, J = 6.7 Hz), 1.14 (s, 3H), 1.09-2.00 (m, 16H), 1.07 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H).

Compound TX63797: LiBr (1.20 g, 13.82 mmol) was added to a mixture of **TX63749** (684 mg, 1.39 mmol), NaOAc (280 mg, 3.41 mmol) and DMAc (14 mL) at room temperature. The heterogeneous mixture was heated at 150 °C with N_2 bubbled through for 6 h. The reaction was cooled, and was diluted with EtOAc. The mixture was transferred to a seperatory funnel, which was washed with 1N aq. HCl, and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-30% EtOAc in hexanes, and then, 0-5% MeOH in CH_2Cl_2) to give compound **TX63797** (404 mg, 61% yield) as a white solid: m/z = 480.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 2.80 (m, 1H), 2.76 (d, 1H, J = 3.9 Hz), 2.51 (dd, 1H, J = 4.5, 16.4 Hz), 2.35-2.47 (m, 2H), 1.20 (d, 3H, J = 6.7 Hz), 1.15-2.05 (m, 16H), 1.15 (s, 3H), 1.12 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H).

Compound 30: Oxalyl chloride (0.22 mL, 2.60 mmol) and catalytic amount of DMF were added sequentially to a solution of **TX63797** (407 mg, 0.85 mmol) in CH_2Cl_2 (17 mL) at 0 °C. After the reaction was stirred at ambient temperature for 2 h, it was concentrated on a rotary evaporator. The residue was azeotroped with toluene (3 × 10 mL) to remove residual oxalyl chloride. Compound **30** (490 mg) was obtained as a light yellow foam solid. Compound **30** was used in the next steps without further purification.

Compound TX63680: $EtNH_2$ (2.0 M solution in THF, mL, mmol) was added to a solution of compound **30** (mg, mmol) in CH_2Cl_2 (mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction was transferred to a separatory funnel, which was washed with water. The organic extract was dried with Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give **TX63680** (18 mg, 88% yield) as a white solid: m/z = 507.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 5.66 (t, 1H, J = 5.4 Hz), 3.33 (m, 2H), 2.87 (d, 1H, J = 3.9 Hz), 2.75 (m, 1H), 2.50 (dd, 1H, J = 4.5, 16.2 Hz), 2.34-2.47 (m, 2H), 1.94-2.10 (m, 3H), 1.72-1.84 (m, 3H), 1.14-1.65 (m, 13H), 1.21 (d, 3H, J = 6.7 Hz), 1.16 (s, 3H), 1.11 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H).

Compound 31: NaOMe (71 μL, 0.31 mmol) was added to a mixture of compound **27** (100 mg, 0.21 mmol) and MeOH (2.1 mL) at room temperature. After the reaction was heated at 55 °C for 10 min, THF (0.4 mL) was added. The reaction was heated for another 2 h, and was cooled to room temperature. MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq.

HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-30% EtOAc in hexanes) to give compound **31** (95 mg, 95% yield) as a white solid: m/z = 480.3 (M+1).

Compounds TX63779 and TX63795: DDQ (47 mg, 0.21 mmol) was added to a solution of compound **31** (95 mg, 19.8 mmol) in benzene (2 mL) at room temperature. After the reaction was refluxed for 20 min, it was cooled to room temperature. MTBE was added. The mixture was transferred to a seperatory funnel, which was washed with aq. $NaHCO_3$ until the organic layer was almost colorless. The organic extract was separated, dried with $MgSO_4$, and filtered through a pad of silica gel, which was eluted with EtOAc/hexanes (1/1). The filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (0.5 mL), and was treated with Ac_2O (0.1 mL, 1.06 mmol), pyridine (0.2 mL, 2.48 mmol) and catalytic amount of DMAP. After the reaction was stirred at room temperature for 20 min, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. $NaHCO_3$, and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-25% EtOAc in hexanes) to give compound **TX63779** (26 mg, 27% yield) as a white solid: m/z = 478.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 5.36 (t, 1H, *J* = 3.4 Hz), 3.64 (s, 3H), 2.91 (m, 1H), 2.44 (m, 1H), 1.87-2.18 (m, 4H), 1.07-1.75 (m, 14H), 1.21 (s, 3H), 1.20 (d, 3H, *J* = 6.8 Hz), 1.14 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.85 (s, 3H).

From the column, also get compound **TX63795** (44 mg, 43% yield) as a white solid: m/z = 522.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (t, 1H, *J* = 3.4 Hz), 3.63 (s, 1H), 2.89 (m, 1H), 2.25 (s, 3H), 2.22 (m, 1H), 1.86-2.08 (m, 4H), 1.00-1.74 (m, 18H), 1.13 (s, 3H), 1.06 (d, 3H, *J* = 6.8 Hz), 0.96 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.78 (s, 3H).

Compound TX63807: $CF_3CH_2NH_2$ (19 μL, 0.24 mmol) was added to a solution of compound **30** (40 mg, 0.08 mmol) in CH_2Cl_2 (0.80 mL) at 0 °C. After stirring at ambient temperature for 2 h, the reaction mixture was purified by column chromatography (silica gel, eluting with 0% to 15% EtOAc in CH_2Cl_2) to give **TX63807** (28 mg, 62% yield) as a white solid: m/z = 561.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.93 (t, 1H, *J* = 6.3 Hz), 4.08 (m, 1H), 3.84 (m, 1H), 2.84 (d, 1H, *J* = 4.1 Hz), 2.78 (m, 1H), 2.49 (dd, 1H, *J* = 4.6, 16.3 Hz), 2.34-2.47 (m,

2H), 2.11 (ddd, 1H, J = 4.0, 14.2, 14.2 Hz), 1.98 (m, 2H), 1.22-1.85 (m, 13H), 1.21 (d, 3H, J = 6.8 Hz), 1.15 (s, 3H), 1.07 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H).

Compound TX63811: Imidazole (16 mg, 0.24 mmol) was added to a solution of compound **30** (40 mg, 0.08 mmol) in benzene (0.80 mL) at 0 °C. After stirring at ambient temperature for 2 h, the reaction mixture was purified by column chromatography (silica gel, eluting with 0% to 65% EtOAc in hexanes) to give **TX63811** (34 mg, 80% yield) as a white solid: m/z = 530.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.64 (s, 1H), 7.60 (s, 1H), 7.09 (s, 1H), 2.99 (m, 1H), 2.95 (d, 1H, J = 4.1 Hz), 2.51 (dd, 1H, J = 4.6, 16.4 Hz), 2.34-2.47 (m, 2H), 2.26 (ddd, 1H, J = 3.6, 14.3, 14.3 Hz), 2.10 (m, 1H), 1.93-2.03 (m, 3H), 1.72-1.92 (m, 3H), 1.30-1.62 (m, 8H), 1.19 (d, 3H, J = 6.7 Hz), 1.15 (s, 3H), 1.04 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H).

Compound TX63812: Morpholine (27 μL, 0.25 mmol) was added to a solution of compound **30** (40 mg, 0.08 mmol) in CH_2Cl_2 (0.80 mL) at 0 °C. After stirring at ambient temperature for 1 h, the reaction mixture was purified by column chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give **TX63812** (30 mg, 68% yield) as a white solid: m/z = 549.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 1H), 3.61-3.77 (m, 8H), 3.16 (bs, 1H), 2.92 (m, 1H), 2.34-2.50 (m, 3H), 1.95-2.10 (m, 3H), 1.12-1.85 (m, 13H), 1.21 (d, 3H, J = 6.7 Hz), 1.15 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H).

Compound TX63814: Et_3N (56 μL, 0.40 mmol) and NH_2OH-HCl (21 mg, 0.30 mmol) were added sequentially to a solution of compound **30** (50 mg, 0.10 mmol) in THF (1 mL) and water (0.1 mL) at room temperature. After the reaction was stirred for 1 h, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give **TX63814** which was contaminated with some impurities. The compound was purified again by column chromatography (silica gel, eluting with 0% to 5% MeOH in CH_2Cl_2) to give **TX63814** (24 mg, 48% yield) as a white solid: m/z = 495.2 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.65 (s, 1H), 7.42 (bs, 1H), 2.79 (d, 1H, J = 4.1 Hz), 2.75 (m, 1H), 2.52 (dd, 1H, J = 4.5, 16.4 Hz), 2.35-2.48 (m, 2H), 1.72-2.14 (m, 6H), 1.21-1.63 (m, 10H), 1.21 (d, 3H, J = 6.7 Hz), 1.15 (s, 3H), 1.11 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H).

Compound TX63815: Et_3N (56 μL, 0.40 mmol) and NH_2OMe-HCl (25 mg, 0.30 mmol) were added sequentially to a solution of compound **30** (50 mg, 0.10 mmol) in THF (1 mL) and water (0.1 mL) at room temperature. After the reaction was stirred for 1 h, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 65% EtOAc in hexanes) to give **TX63815** (31 mg, 61% yield) as a white solid: m/z = 509.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.65 (s, 1H), 3.77 (s, 3H), 2.87 (d, 1H, *J* = 4.1 Hz), 2.73 (m, 1H), 2.35-2.53 (m, 3H), 1.75-2.10 (m, 6H), 1.22-1.63 (m, 10H), 1.21 (d, 3H, *J* = 6.7 Hz), 1.15 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H).

Compound TX63816: NH_3 (2.0 M in MeOH, 0.45 mL, 0.90 mmol) was added to a solution of compound **30** (150 mg, 0.30 mmol) in MTBE (3 mL) and CH_2Cl_2 (3 mL) at 0 °C. The reaction was stirred at 0 °C, and then, at room temperature for 1 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with water, 1 N aq. HCl, and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give **TX63816** (120 mg, 83% yield) as a white solid: m/z = 479.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 5.64 (bs, 1H), 5.30 (bs, 1H), 2.91 (d, 1H, *J* = 4.1 Hz), 2.72 (m, 1H), 2.35-2.53 (m, 3H), 1.76-2.10 (m, 6H), 1.22-1.63 (m, 10H), 1.21 (d, 3H, *J* = 6.7 Hz), 1.16 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H).

Compound TX63817: Et_3N (65 μL, 0.47 mmol) and TFAA (39 μL, 0.28 mmol) were added sequentially to a solution of **TX63816** (90 mg, 0.19 mmol) in CH_2Cl_2 (1.9 mL) at 0 °C. After the reaction was stirred at 0 °C for 30 min, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give **TX63817** (65 mg, 75% yield) as a white solid: m/z = 461.3 (M+1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 3.05 (d, 1H, *J* = 4.2 Hz), 2.42-2.59 (m, 4H), 1.98-2.21 (m, 4H), 1.94 (m, 1H), 1.74-1.86 (m, 2H), 1.45-1.65 (m, 5H), 1.34 (s, 3H), 1.15-1.32 (m, 4H), 1.22 (d, 3H, *J* = 6.7 Hz), 1.20 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H).

Compound TX63842: A mixture of DBU (14 μL, 0.09 mmol), EtI (6.7 μL, 0.08 mmol), compound **TX63797** (40 mg, 0.083 mmol) and toluene (0.83 mL) was heated at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was purified by column chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give **TX63842** (26 mg, 61% yield) as a white solid: m/z = 508.4 (M+1), 434.2 (M-CO_2Et); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 4.17 (m, 2H), 2.82 (m, 1H), 2.72 (d, 1H, *J* = 4.2 Hz), 2.49 (dd, 1H, *J* = 4.7, 16.3 Hz), 2.43 (m, 1H), 2.37 (dd, 1H, *J* = 13.5, 16.0 Hz), 1.99 (dd, 1H, *J* = 4.5, 13.4 Hz), 1.87-1.96 (m, 2H), 1.76-1.83 (m, 2H), 1.40-1.72 (m,7H), 1.33 (ddd, 1H, *J* = 4.4, 13.9, 13.9 Hz), 1.26 (t, 3H, *J* = 7.1 Hz), 1.20 (d, 3H, *J* = 6.8 Hz), 1.15 (s, 3H), 1.10-1.26 (m, 3H), 1.09 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H).

Compound TX63843: *n*-$BuNH_2$ (30 μL, 0.30 mmol) was added to a solution of compound **30** (50 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After the reaction was stirred at 0 °C for 30 min, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl, and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give **TX63843** (37 mg, 69% yield) as a white solid: m/z = 535.3 (M+1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 5.65 (t, 1H, *J* = 5.7 Hz), 3.25 (m, 2H), 2.86 (d, 1H, *J* = 4.2 Hz), 2.75 (m, 1H), 2.48 (dd, 1H, *J* = 4.6, 16.3 Hz), 2.43 (m, 1H), 2.37 (dd, 1H, *J* = 13.6, 16.2 Hz), 1.92-2.08 (m, 3H), 1.71-1.82 (m, 3H), 1.20 (d, 3H, *J* = 6.8 Hz), 1.15 (s, 3H), 1.10-1.62 (m, 14H), 1.09 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.93 (t, 3H, *J* = 7.4 Hz), 0.92 (s, 3H).

Compound 32: DIBAL-H (1.0 M solution in toluene, 7.3 mL, 7.30 mmol) was added to a solution of compound **27** (1.00 g, 2.08 mmol) in THF (20 mL) at 0 °C. After the reaction was stirred at 0 °C for 2 h, water (1 mL) and 1 N aq. HCl (50 mL) were added sequentially. The mixture was transferred to a separatory funnel, which extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **32** (0.90 g, 96% yield) as a white solid: m/z = 452.3 (M+1).

Compound 33: Ac_2O (0.8 mL, 8.47 mmol) and DMAP (10 mg, 0.08 mmol) were added to a solution of compound **32** (400 mg, 0.88 mmol) in pyridine (1.6 mL) at room temperature. After the reaction was stirred at room temperature for 10 min,

aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with 1N aq. HCl, aq. $NaHCO_3$, water, and was dried with $MgSO_4$. The solution was filtered through a pad of silica gel, and was concentrated to give compound **33** (420 mg, 96% yield) as a white solid: m/z = 494.3 (M+1).

Compound 34: AcO_2H (39% in AcOH, 210 μL, 1.62 mmol) was added to a solution of compound **33** (533 mg, 1.08 mmol) in AcOH (5.4 mL) at room temperature. After heated at 55 °C for 7 h, additional amount of AcO_2H (39% in AcOH, 100 μL, 0.77 mmol) was added. After another 13 h, the reaction was cooled to room temperature, and was treated with aq. Na_2SO_3. The product was extracted with CH_2Cl_2. The combined organic extracts were washed with aq. Na_2SO_3, and aq. $NaHCO_3$, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-40% EtOAc in hexanes) to give compound **34** (440 mg, 80% yield) as a white solid: m/z = 510.3 (M+1).

Compound 35: NaOMe (0.35 mL, 1.53 mmol) was added to a mixture of compound **34** (315 mg, 0.62 mmol) and MeOH (6 mL) at room temperature. After heated at 55 °C for 2 h, the reaction was cooled to room temperature. MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-70% EtOAc in hexanes) to give compound **35** (290 mg, 99% yield) as a white solid: m/z = 468.3 (M+1).

Compound TX63839: A solution of 1,3-dibromo-5,5-dimethylhydantoin (81 mg, 0.28 mmol) in DMF (1.5 mL) was added to a solution of compound **35** (290 mg, 0.62 mmol) in DMF (1.5 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (200 μL, 2.48 mmol) was added. The reaction was heated at 55 °C for another 1.5 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl, aq. Na_2SO_3, and water. The organic extract was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 65% EtOAc in hexanes) to give **TX63839** (235 mg, 81% yield) as a white solid: m/z = 466.3 (M+1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 3.51 (d, 2H, *J* = 6.0 Hz), 2.71 (d, 1H, *J* = 4.2 Hz), 2.52 (dd, 1H, *J* = 4.6, 16.6 Hz), 2.45 (m, 1H), 2.39 (dd, 1H, *J* = 13.5, 16.4 Hz), 2.21 (m, 1H), 2.03 (dd, 1H, *J* = 4.7, 13.6 Hz), 1.43-1.90 (m, 8H), 1.24 (s, 3H), 1.21 (d, 3H, *J* =

6.7 Hz), 1.22-1.34 (m, 6H), 1.17 (s, 3H), 1.14 (m, 1H), 1.05 (m, 1H), 0.99 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H).

Compound TX63840: Ac_2O (50 μL, 0.47 mmol) and catalytic amount of DMAP were added to a solution of compound **TX63839** (25 mg, 0.05 mmol) and pyridine (0.2 mL) in CH_2Cl_2 (0.5 mL) at room temperature. After the reaction was stirred at room temperature for 10 min, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with 1N aq. HCl, aq. $NaHCO_3$, water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 10% EtOAc in CH_2Cl_2) to give **TX63840** (28 mg, 99% yield) as a white solid: m/z = 508.3 (M+1), 448.2 (M-OAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (s, 1H), 4.13 (d, 1H, *J* = 11.1 Hz), 3.88 (d, 1H, *J* = 11.1 Hz), 2.79 (d, 1H, *J* = 4.3 Hz), 2.51 (dd, 1H, *J* = 4.6, 16.5 Hz), 2.37-2.48 (m, 2H), 2.19 (m, 1H), 2.08 (s, 3H), 2.02 (dd, 1H, *J* = 4.7, 13.3 Hz), 1.94 (m, 1H), 1.73-1.85 (m, 4H), 1.43-1.64 (m, 4H), 1.28 (s, 3H), 1.21 (d, 3H, *J* = 6.7 Hz), 1.18-1.33 (m, 4H), 1.17 (s, 3H), 1.03-1.08 (m, 2H), 0.98 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H).

Compound TX63841: TFAA (26 μL, 0.18 mmol) was added to a solution of compound **TX63839** (43 mg, 0.09 mmol) and Et_3N (39 μL, 0.28 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$, and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give **TX63841** (45 mg, 87% yield) as a white solid: m/z = 562.3 (M+1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 4.29 (s, 2H), 2.71 (d, 1H, *J* = 4.3 Hz), 2.53 (dd, 1H, *J* = 4.6, 16.6 Hz), 2.38-2.48 (m, 2H), 2.18 (m, 1H), 1.94-2.05 (m, 2H), 1.69-1.89 (m, 4H), 1.45-1.65 (m, 4H), 1.28 (s, 3H), 1.22 (d, 3H, *J* = 6.7 Hz), 1.18 (s, 3H), 1.09-1.33 (m, 6H), 1.00 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H).

Compound TX63858: Methyl triflate (17 μL, 0.15 mmol) was added to a solution of compound **TX63839** (40 mg, 0.09 mmol) and 2,6-di-t-butyl-4-methylpyridine (35 mg, 0.17 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After stirring at ambient temperature for 16 h, the reaction was quenched with the addition of aq. $NaHCO_3$. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with 1 N aq. HCl, aq. $NaHCO_3$, and

water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give **TX63858** (31 mg, 75% yield) as a white solid: m/z = 480.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 3.34 (s, 3H), 3.24 (d, 1H, *J* = 9.1 Hz), 3.20 (d, 1H, *J* = 9.1 Hz), 2.80 (d, 1H, *J* = 4.1 Hz), 2.38-2.56 (m, 3H), 2.27 (m, 1H), 2.06 (dd, 1H, *J* = 4.6, 13.1 Hz), 1.72-1.92 (m, 5H), 1.46-1.68 (m, 4H), 1.28 (s, 3H), 1.24 (d, 3H, *J* = 6.8 Hz), 1.02-1.34 (m, 6H), 1.20 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H).

Compound TX63859: A mixture of compound **TX63839** (85 mg, 0.18 mmol), DMSO (2.2 mL), AcOH (2.2 mL) and Ac_2O (1.1 mL) was stirred at room temperature for 2 h. The reaction mixture was added slowly to a solution of saturated aq. $NaHCO_3$ (80 mL) at room temperature. After stirring for 40 min, the mixture was transferred to a separatory funnel, which was extracted with CH_2Cl_2. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give **TX63859** (77 mg, 80% yield) as a white solid: m/z = 478.3 (M-MeS); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 4.67 (d, 1H, *J* = 11.4 Hz), 4.61 (d, 1H, *J* = 11.4 Hz), 3.45 (d, 1H, *J* = 9.0 Hz), 3.31 (d, 1H, *J* = 9.0 Hz), 2.88 (d, 1H, *J* = 4.1 Hz), 2.30-2.56 (m, 4H), 2.13 (s, 3H), 2.06 (m, 1H), 1.76-1.96 (m, 5H), 1.46-1.67 (m, 4H), 1.32 (s, 3H), 1.24 (d, 3H, *J* = 6.8 Hz), 1.03-1.35 (m, 6H), 1.21 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H).

Compound TX63860: DAST (24 μL, 0.18 mmol) was added to a mixture of compound **TX63859** (63 mg, 0.12 mmol), NBS (32 mg, 0.18 mmol) and 4Å MS in CH_2Cl_2 (1.5 mL) at 0 °C. After stirring for 50 min, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with aq. Na_2SO_3, aq. $NaHCO_3$, and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give **TX63860** (31 mg, 52% yield) as a white solid: m/z = 478.3 (M-F); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 5.28 (m, 2H), 3.65 (d, 1H, *J* = 8.8 Hz), 3.52 (d, 1H, *J* = 8.7 Hz), 2.75 (d, 1H, *J* = 4.3 Hz), 2.37-2.58 (m, 3H), 2.32 (m, 1H), 2.05 (dd, 1H, *J* = 4.7, 13.2 Hz), 1.93 (ddd, 1H, *J* = 4.8, 13.9, 13.9 Hz), 1.74-1.87 (m, 4H), 1.46-1.67 (m, 4H), 1.27 (s, 3H), 1.24 (d, 3H, *J* = 6.7 Hz), 1.05-1.35 (m, 6H), 1.20 (s, 3H), 1.01 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H).

Compound 36: DCC (171 mg, 0.83 mmol) and DMAP (26 mg, 0.21 mmol) were added to a solution of compound **13** (300 mg, 0.63 mmol) and 3-hydroxy-4-methyl-2(3*H*)-thiazolethione (123 mg, 0.84 mmol) in CH_2Cl_2 successively at room temperature. After stirring for 5 h, hexanes (2 mL) was added. The mixture was filtered. The precipitate was washed with CH_2Cl_2/hexanes (1:1, 10 mL). The combined filtrate and washes were concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **36** (305 mg, 80% yield) as a white solid: m/z = 434.2 (M- $C_5H_4NO_2S_2$). Compound **36** was contaminated with some *N*,*N*'-dicyclohexylurea, and was used in the next step without further purification.

Compound 37: Bu_3SnH (0.33 mL, 1.24 mmol) and AIBN (9 mg, 0.05 mmol) were added to a solution of compound **36** (305 mg, 0.50 mmol) in benzene (20 mL) at room temperature. The reaction was heated at reflux for 25 min. After the reaction was cooled to room temperature, the mixture was purified by column chromatography (silica gel, eluting with 0% to 20% EtOAc in hexanes) to give purified compound **37** (84 mg, 38% yield) as a white solid. From the column, also get a second crop of compound **37** (111 mg, 51% yield) which was contaminated with some impurities. Compound **37**: m/z = 436.3 (M+1).

Compound 38: NaOMe (66 μL, 0.29 mmol) was added to a mixture of compound **37** (84 mg, 0.19 mmol) and MeOH (1.9 mL) at room temperature. After the reaction was heated at 55 °C for 1 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **38** (86 mg, 99% yield) as a white solid: m/z = 436.3 (M+1).

Compound TX63869: A solution of DBDMH (28 mg, 0.10 mmol) in DMF (0.5 mL) was added to a solution of cyanoketone **38** (86 mg, 0.20 mmol) in DMF (0.5 mL) at 0 °C. After stirring at 0 °C for 1 h, pyridine (48 μL, 0.59 mmol) was added. The reaction was heated at 55 °C for 2 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give compound **TX63869** (72 mg, 84% yield) as a white solid: m/z = 434.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.04

(s, 1H), 2.75 (d, 1H, J = 4.7 Hz), 2.57 (m, 1H), 2.48 (m, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.26 (d, 3H, J = 6.7 Hz), 1.10-1.92 (m, 16 H), 1.00 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H).

Compound 39: A mixture of compound **13** (600 mg, 1.21 mmol), DDQ (305 mg, 1.34 mmol) and toluene (12 mL) was heated at 115 °C in a Biotage microwave reactor for 3 h. CH_2Cl_2 was added. The mixture was transferred to a separatory funnel, which was washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **39** (272 mg, 47% yield) as a white solid: m/z = 478.3 (M+1).

Compound 40: Compound **39** (180 mg, 0.38 mmol) was dissolved in EtOH (4.8 mL), THF (2.4 mL) and water (0.6 mL). NaOH (2.5 N aq. solution, 0.75 mL, 1.88 mmol) was added at room temperature. After stirring for 6 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated to give compound **40** (180 mg) as a white solid: m/z = 478.3 (M-17). Compound **40** was used in the next steps without further purification.

Compound 41: Compound **40** (80 mg, 0.16 mmol) was dissolved in toluene (1.2 mL) and MeOH (0.4 mL), and the mixture was cooled to -20 °C. $TMSCHN_2$ (2.0 M solution in ether, 96 μL, 0.19 mmol) was added dropwise. After stirring for 10 min, AcOH and EtOAc were added successively. The mixture was transferred to a separatory funnel, which was washed with aq. $NaHCO_3$. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **41** (36 mg, 42% yield from **39**) as a white solid: m/z = 492.3 (M-17).

Compound TX63870: A solution of DBDMH (10 mg, 0.035 mmol) in DMF (0.17 mL) was added to a solution of compound **41** (36 mg, 0.07 mmol) in DMF (0.18 mL) at 0 °C. After stirring at 0 °C for 1 h, pyridine (17 μL, 0.21 mmol) was added. The reaction was heated at 55 °C for 2 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 40% EtOAc in hexanes) to give compound **TX63870**, which was contaminated with some impurities. The product was purified again by PTLC (silica

gel, eluting with 40% EtOAc in hexanes) to give purified **TX63870** (26 mg, 72% yield) as a white solid: m/z = 490.3 (M-17); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.05 (s, 1H), 3.70 (s, 3H), 2.90 (m, 1H), 2.47 (m, 1H), 2.23 (m, 1H), 1.67-2.00 (m, 7H), 1.55 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.25 (d, 3H, *J* = 6.8 Hz), 1.04 (s, 3H), 0.99 (s, 3H), 0.95-1.45 (m, 7H), 0.89 (s, 3H).

Compound 42: Compound **40** (100 mg, 0.20 mmol) was dissolved in MTBE (2 mL) and $CHCl_3$ (2 mL), and the solution was cooled to 0 °C. CH_3CHN_2 (1.0 M solution in MTBE, prepared in situ from N-nitroso-N-ethylurea and KOH) was added dropwise until compound **40** was completely consumed. Nitrogen was bubbled through the reaction for 5 min to blow out the excess CH_3CHN_2. The mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **42** (19 mg, 18% yield from **39**) as a white solid: m/z = 506.3 (M-17).

Compound TX63901: A solution of DBDMH (5.2 mg, 0.018 mmol) in DMF (0.09 mL) was added to a solution of compound **42** (19 mg, 0.036 mmol) in DMF (0.09 mL) at 0 °C. After stirring at 0 °C for 1 h, pyridine (9 μL, 0.11 mmol) was added. The reaction was heated at 55 °C for 2 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by PTLC (silica gel, eluting with 33% EtOAc in hexanes) to give compound **TX63901** (13 mg, 68% yield) as a white solid: m/z = 504.3 (M-17); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 6.05 (s, 1H), 4.25 (m, 1H), 4.11 (m, 1H), 2.90 (m, 1H), 2.47 (m, 1H), 2.24 (m, 1H), 1.97 (m, 1H), 1.67-1.89 (m, 6H), 1.55 (m, 1H), 1.50 (s, 3H), 1.47 (s, 3H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.25 (d, 3H, *J* = 6.8 Hz), 1.04 (s, 3H), 0.99 (s, 3H), 0.95-1.47 (m, 7H), 0.89 (s, 3H).

Compound 43: $LiAlH_4$ (2.0 M in THF, 0.73 mL, 1.46 mmol) was added to a solution of compound **39** (350 mg, 0.73 mmol) in THF (7 mL) at 0 °C. After stirring at 0 °C for 3 h, the reaction was quenched by water. EtOAc and 1 N aq. HCl were added. After stirring at room temperature for 10 min, the mixture was transferred to a separatory funnel. The organic extract was separated, washed with water, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 70% EtOAc in hexanes) to give compound **43** (165 mg, 47% yield) as a white solid: m/z = 484.3 (M+1).

Compounds 44 and 45: Ac_2O (40 μL, 0.42 mmol) was added to a solution of compound **43** (163 mg, 0.34 mmol), pyridine (136 μL, 1.68 mmol) and DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (3.3 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with 1N aq. HCl, aq. $NaHCO_3$ and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **44** (133 mg, 75% yield) as a white solid: m/z = 526.3 (M+1). From the column, also get some compound **43** and **45** (overall 58 mg).

Compound 46: NaOMe (82 μL, 0.36 mmol) was added to a solution of compound **43** and **45** (58 mg) obtained from the last reaction in MeOH (1.2 mL) at room temperature. After the reaction was heated at 55 °C for 1 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 60% EtOAc in hexanes) to give compound **46** (33 mg, 60%) as a white solid: m/z = 466.3 (M-17), 448.3.

Compound TX63904: A solution of DBDMH (9.5 mg, 0.033 mmol) in DMF (0.16 mL) was added to a solution of compound **46** (32 mg, 0.066 mmol) in DMF (0.17 mL) at 0 °C. After Stirring at 0 °C for 1 h, pyridine (16 μL, 0.20 mmol) was added. The reaction was heated at 55 °C for 3 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **TX63904** (28 mg, 88% yield) as a white solid: m/z = 446.3 (M-35); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 5.50 (d, 1H, *J* = 2.2 Hz), 4.28 (dd, 1H, *J* = 2.1, 8.4 Hz), 3.92 (d, 1H, *J* = 10.6 Hz), 3.55 (d, 1H, *J* = 10.6 Hz), 3.13 (b, 1H), 2.40 (m, 1H), 2.29 (m, 1H), 2.13 (d, 1H, *J* = 8.5 Hz), 1.89 (m, 1H), 1.46 (s, 6H), 1.19 (d, 3H, *J* = 6.7 Hz), 1.00-1.80 (m, 15H), 1.02 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H).

Compound 47: A mixture of compound **44** (132 mg, 0.25 mmol), NMO (45 mg, 0.38 mmol) and 4 Å MS in CH_2Cl_2 (5 mL) was stirred at room temperature for 10 min. TPAP (9 mg, 0.025 mmol) was added. After the reaction was stirred at room temperature for 3 h, aq. Na_2SO_3 was added. The mixture was transferred to a

separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, and was filtered through a pad of celite. The filtrate was dried with $MgSO_4$, and was concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 10% EtOAc in CH_2Cl_2) to give compound **47** (95 mg, 72% yield) as a white solid: m/z = 524.3 (M+1), 508.3.

Compound 48: NaOMe (103 μL, 0.45 mmol) was added to a solution of compound **47** (94 mg, 0.18 mmol) in MeOH (1.8 mL) at room temperature. After the reaction was heated at 55 °C for 2 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **48** (77 mg, 89% yiled) as a white solid: m/z = 464.3 (M-17).

Compound TX63908: A solution of DBDMH (23 mg, 0.080 mmol) in DMF (0.4 mL) was added to a solution of compound **48** (77 mg, 0.16 mmol) in DMF (0.4 mL) at 0 °C. After Stirring at 0 °C for 1 h, pyridine (39 μL, 0.48 mmol) was added. The reaction was heated at 55 °C for 1.5 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **TX63908** (66 mg, 86% yield) as a white solid: m/z = 462.2 (M-17); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.04 (s, 1H), 4.12 (d, 1H, *J* = 9.9 Hz), 3.40 (d, 1H, *J* = 9.9 Hz), 2.89 (bs, 1H), 2.47 (m, 1H), 2.34 (m, 1H), 2.12 (m, 1H), 1.69-1.88 (m, 7H), 1.58 (s, 3H), 1.49 (s, 3H), 1.48 (m, 1H), 1.25 (d, 3H, *J* = 6.7 Hz), 1.05-1.35 (m, 6H), 1.01 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H).

Compound TX63909: Ac_2O (26 μL, 0.28 mmol) and DMAP (1 mg, 0.008 mmol) were added to a solution of compound **TX63908** (32 mg, 0.067 mmol) and pyridine (54 μL, 0.67 mmol) in CH_2Cl_2 (1 mL) at room temperature. After the reaction was stirred at room temperature for 30 min, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with 1N aq. HCl, aq. $NaHCO_3$, and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **TX63909** (30 mg, 94% yield) as a white solid: m/z = 504.3 (M-17); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 8.08 (s, 1H), 6.06 (s, 1H), 4.39 (d, 1H, J = 10.7 Hz), 4.32 (d, 1H, J = 10.7 Hz), 2.48 (m, 1H), 2.11 (s, 3H), 2.08-2.15 (m, 2H), 1.88 (m, 1H), 1.70-1.82 (m, 6H), 1.58 (m, 1H), 1.56 (s, 3H), 1.50 (s, 3H), 1.44 (m, 1H), , 1.26 (d, 3H, J = 6.7 Hz), 1.10-1.39 (m, 6H), 1.04 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H).

Compounds 49 and 50: $LiAlH_4$ (2.0 M in THF, 0.10 mL, 0.20 mmol) was added to a solution of compound **39** (200 mg, 0.42 mmol) in THF (4 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched by water. EtOAc and 1 N aq. HCl were added. After stirring at room temperature for 10 min, the mixture was transferred to a separatory funnel. The organic extract was washed with water, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give a mixture of compound **49** and **50** (3:1 ratio, 145 mg, 72% yield) as a white solid. Compound **49**: m/z = 482.3 (M+1). Compound **50**: m/z = 480.3 (M+1).

Compounds 51 and 52: A solution of compound **49** and **50** (145 mg, 0.30 mmol) in CH_2Cl_2 (6 mL) was cooled to 0 °C. DAST (59 μL, 0.45 mmol) was added. After the reaction was stirred at ambient temperature for 20 min, aq. $CaCl_2$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give a mixture of compound **51** and **52** (66 mg) as a white solid.

Compound 52: The mixture of compound **51** and **52** was dissolved in acetone (3 mL), and was cooled to 0 °C. Jones' reagent was added dropwise until the orange color persisted. After the reaction was stirred at 0 °C for 10 min, i-PrOH was added. After stirring for another 5 min at room temperature, the reaction was diluted with EtOAc. The mixture was transferred to a seperatory funnel, which was washed with water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 25% EtOAc in hexanes) to give compound **52** (57 mg, 39% yield from **49** and **50**) as a white solid: m/z = 482.2 (M+1).

Compound 53: NaOMe (41 μL, 0.18 mmol) was added to a solution of compound **52** (57 mg, 0.12 mmol) in MeOH (1.2 mL) and THF (0.6 mL) at room temperature. After the reaction was heated at 55 °C for 1 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl

and water. The organic extract was dried with $MgSO_4$, and concentrated to give compound **53** (57 mg) as a white solid: m/z = 482.2 (M+1).

Compound TX63907: A solution of DBDMH (17 mg, 0.059 mmol) in DMF (0.30 mL) was added to a solution of compound **53** (57 mg, 0.12 mmol) in DMF (0.29 mL) at 0 °C. After Stirring at 0 °C for 1 h, pyridine (29 μL, 0.36 mmol) was added. The reaction was heated at 55 °C for 1.5 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 45% EtOAc in hexanes) to give compound **TX63907** (46 mg, 81% yield from **52**) as a white solid: m/z = 480.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 5.84 (dd, 1H, *J* = 2.6, 12.2 Hz), 5.09 (dd, 1H, *J* = 2.6, 45.1 Hz), 2.56 (m, 1H), 2.46 (m, 1H), 2.19 (m, 1H), 1.44 (s, 3H), 1.30-1.85 (m, 14 H), 1.25 (s, 3H), 1.25 (d, 3H, *J* = 6.3 Hz), 0.99 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H).

Compound 54: A solution of pyridinium tribromide (311 mg, 0.88 mmol) in MeCN (3 mL) was added to a solution of compound **34** (388 mg, 0.76 mmol) in MeCN (4.6 mL) at room temperature. After the reaction was stirred for 2 h, additional amount of pyridinium tribromide (62 mg, 0.17 mmol) in MeCN (1 mL) was added. The reaction was stirred for another 1 h. Aq. Na_2SO_3 was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The combined organic extracts were washed with 1 N aq. HCl and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **54** (256 mg, 66% yield) as a white solid.

Compounds 55 and 56: $LiAlH_4$ (2.0 M in THF, 0.25 mL, 0.50 mmol) was added to a solution of compound **54** (250 mg, 0.49 mmol) in THF (4.9 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, additional amount of $LiAlH_4$ (2.0 M in THF, 0.25 mL, 0.50 mmol) was added. The reaction was continued stirring for another 1 h. Water was added. The mixture was stirred at room temperature for 5 min. EtOAc and 1 N aq. HCl were added. The mixture was transferred to a separatory funnel. The organic extract was washed with water, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **55** (106 mg, 46% yield). From the column, also get compound **56** (107 mg, 46% yield).

Compound 57: Compound **55** (103 mg, 0.21 mmol) and **56** (60 mg, 0.12 mmol), NMO (82 mg, 0.70 mmol), 4 Å MS and CH_2Cl_2 (9 mL) were stirred at room temperature for 10 min. TPAP (16 mg, 0.045 mmol) was added. After stirring at room temperature for 1 h, the mixture was filtered through a silica gel plug, which was washed with CH_2Cl_2/EtOAc (2:1). The combined filtrate and washes were transferred to a separatory funnel, which was washed with 1 N HCl and water. The organic extract was dried with $MgSO_4$, and was concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes) to give compound **57** (140 mg, 86% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, 1H, J = 1.1 Hz), 8.08 (s, 1H), 5.93 (s, 1H), 2.84 (m, 1H), 2.75 (d, 1H, J = 15.4 Hz), 2.71 (d, 1H, J = 4.7 Hz), 2.55 (m, 1H), 2.41 (m, 1H), 1.94 (m, 1H), 1.88 (m, 1H), 1.75 (m, 1H), 1.39 (d, 3H, J = 6.8 Hz), 1.28 (s, 3H), 1.07 (s, 3H), 1.15-1.70 (m, 12H), 1.02 (s, 3H), 1.00 (s, 3H), 0.92 (s, 3H).

Compound 58: Compound **57** (133 mg, 0.29 mmol), Na_2HPO_4 (71 mg, 0.5 mmol), m-CPBA (94 mg, 0.42 mmol) in CH_2Cl_2 (5.5 mL) were stirred at room temperature for 6 h. Aq. Na_2SO_3 was added. The mixture was stirred for 5 min, and was transferred to a separatory funnel, which was extracted with CH_2Cl_2. The organic extract was washed with aq. $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **58** (117 mg, 85% yield): m/z = 480.3 (M+1), 434.3.

Compound 59: NaOMe (140 μL, 0.61 mmol) was added to a solution of compound **58** (117 mg, 0.24 mmol) in MeOH (2.4 mL) at room temperature. After the reaction was heated at 55 °C for 1 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 35% acetone in hexanes) to give compound **59** (96 mg, 90% yield) as a white solid: m/z = 452.3 (M+1), 434.3.

Compound TX63925: A solution of DBDMH (30 mg, 0.10 mmol) in DMF (0.5 mL) was added to a solution of compound **59** (96 mg, 0.21 mmol) in DMF (0.5 mL) at 0 °C. After Stirring at 0 °C for 1 h, pyridine (51 μL, 0.63 mmol) was added. The reaction was heated at 55 °C for 2 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and

concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **TX63925** (90 mg, 94% yield) as a white solid: m/z = 450.2 (M+1), 432.2; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.03 (s, 1H), 3.48 (d, 1H, *J* = 4.7 Hz), 2.50 (m, 1H), 2.39 (m, 1H), 2.11 (m, 1H), 1.99 (m, 1H), 1.90 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.27 (d, 3H, *J* = 6.7 Hz), 1.18-1.81 (m, 11H), 1.10 (m, 1H), 1.03 (s, 3H), 1.00 (s, 3H), 0.94 (s, 1H), 0.90 (s, 3H).

Compound TX63928: Ac_2O (30 μL, 0.32 mmol) and BF_3-OEt_2 (15 μL, 0.12 mmol) were added sequentially to a solution of compound **TX63925** (30 mg, 0.067 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C. After the reaction was stirred for 10 min at 0 °C, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$ and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 35% EtOAc in hexanes) to give compound **TX63928** (11 mg, 34% yield) as a white solid: m/z = 432.2 (M-OAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.05 (s, 1H), 3.33 (d, 1H, *J* = 4.7 Hz), 2.72 (m, 1H), 2.49 (m, 1H), 2.42 (m, 1H), 2.37 (m, 1H), 2.02 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.27 (d, 3H, *J* = 6.7 Hz), 1.20-1.95 (m, 12H), 1.16 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H).

Compound TX63929: Trichloroacetyl isocyanate (11 μL, 0.092 mmol) was added to a solution of compound **TX63925** (30 mg, 0.066 mmol) in CH_2Cl_2 (1 mL) at room temperature. After the reaction was stirred for 2 h, the solvent was removed by evaporation to give compound **60**. Compound **60** was dissolved in MeOH (1 mL), and K_2CO_3 (27 mg, 0.20 mmol) was added. After the reaction was stirred at room temperature for 1 h, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give compound **TX63929** (20 mg, 61% yield from **TX63925**) as a white solid: m/z = 432.2 (M-$OCONH_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.06 (s, 1H), 4.47 (bs, 2H), 3.33 (d, 1H, *J* = 4.7 Hz), 2.69 (m, 1H), 2.51 (m, 1H), 2.44 (m, 2H), 1.55-2.00 (m, 9H), 1.49 (s, 3H), 1.48 (s, 3H), 1.28 (d, 3H, *J* = 6.6 Hz), 1.37 (m, 1H), 1.24-1.33 (m, 2H), 1.19 (m, 1H), 1.07 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H).

Compound 61: NaOMe (31 μL, 0.14 mmol) was added to a solution of compound **55** (43 mg, 0.089 mmol) in MeOH (0.89 mL) at room temperature. After

the reaction was heated at 55 °C for 1 h, MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 100% EtOAc in hexanes) to give compound **61** (35 mg, 81% yield) as a white solid.

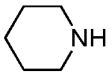
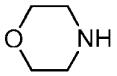
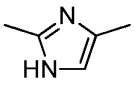
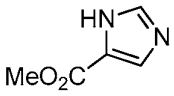
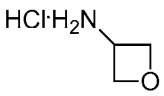
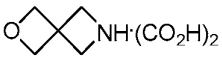
Compound TX63923: A solution of DBDMH (10.7 mg, 0.037 mmol) in DMF (0.37 mL) was added to a solution of compound **61** (35 mg, 0.074 mmol) in DMF (0.37 mL) at 0 °C. After Stirring at 0 °C for 1 h, pyridine (18 μL, 0.22 mmol) was added. The reaction was heated at 55 °C for 3 h. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with 1N aq. HCl, aq. Na_2SO_3 and water. The organic extract was separated, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 65% EtOAc in hexanes) to give compound **TX63923** (28 mg, 80% yield) as a white solid: m/z = 448.3 (M-17), 430.3 (M-35); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 5.72 (d, 1H, *J* = 3.1 Hz), 4.30 (m, 1H), 3.62 (m, 2H), 2.42 (m, 1H), 2.19 (m, 1H), 2.02 (m, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 1.22-1.84 (m, 13H), 1.22 (d, 3H, *J* = 6.7 Hz), 1.14 (m, 1H), 1.04 (m, 1H), 0.98 (s, 3H), 0.95 (s, 3H), 0.89 (s, 3H).

Compound TX63820: Compound **TX63520** (95.5 mg, 0.2 mmol), alkyl iodide (0.2 mmol), DBU (33.5 mg, 0.22 mmol) were dissolved in toluene (2 mL). The reaction mixture was stirred at RT for 21 hr. The reaction mixture was directly loaded on a silica gel column, and purified by column chromatography (silica gel, 0-20 % EtOAc in Hexanes) to give **TX63820** (18.6 mg, 18.4%, only the pure fractions were collected, purification was not optimized). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.02 (s, 1H), 4.12-4.22 (m, 2H), 3.01-3.09 (m, 1H), 2.97 (d, 1H, *J* = 4.5 Hz), 2.43-2.51 (m, 1H), 1.80-1.94 (m, 3H), 1.60-1.79 (m, 5H), 1.46-1.59 (m, 4H), 1.44 (s, 3H), 1.33 (s, 3H), 1.16-1.36 (m, 9H), 1.01 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H); m/z 506 (M+1).

Compound TX63821: Compound **TX63520** (95.5 mg, 0.2 mmol), alkyl iodide (0.2 mmol), DBU (33.5 mg, 0.22 mmol) were dissolved in toluene (2 mL). The reaction mixture was stirred at RT for 18 h, then 80 °C for 2 h. The reaction mixture was directly loaded on a silica gel column, and purified by column chromatography (silica gel, 0-20 % EtOAc in Hexanes) to give **TX73821** (84.1 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.02 (s, 1H), 4.09 (t, 2H, *J* = 6.6 Hz), 2.93-3.10 (m,

1H), 2.96 (d, 1H, *J* = 4.6 Hz), 2.43-2.51 (m, 1H), 1.80-1.94 (m, 3H), 1.40-1.95 (m, 15H), 1.44 (s, 3H), 1.34 (s, 3H), 1.16-1.40 (m, 10H), 1.25 (d, 1H, *J* = 6.7 Hz), 1.01 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H), 0.88 (t, 3H, *J* = 6.8 Hz); m/z 562 (M+1).

Table 2.

Product Name	Substituted Amine (mmol)	Temperature / Time	Yield (%)
TX63878	$HNMe_2$ *2.0 M in THF* (1.0)	80 °C / 3.5 h	63.5
TX63824	$H_2NMe \cdot HCl$ (1.0)	r.t. / 19 h	10
TX63877	H_2N-*n*-C_4H_9 (1.0)	80 °C / 3 h	45.6
TX63823	 (1.0)	r.t. / 1.5 h	60
TX63880	 1.0)	r.t. / 3 h	58
TX63881	 (1.0)	r.t. / 3.5 h	55
TX63822	 (0.6)	See the experiment for details	22
TX64005	 (1.5)	r.t. / 16 h	30
TX63882	$H_2NOMe \cdot HCl$ (1.0)	r.t. / 3.5 h	8.2
TX64006	$H_2NOH \cdot HCl$ (0.9)	r.t. / 20 h	30
TX63825	 (0.6)	r.t. / 19 h	27
TX64007	 (0.66)	r.t. / 5h	34

Compound TX63822: Compound **11** (0.2 mmol) and 2,4-Dimethyl-1H-imidazole (19.2 mg, 0.2 mmol) were taken up in toluene (1 mL), and the mixture was stirred at room temperature for 65 h, no reaction happened. Additional 2,4-Dimethyl-1H-imidazole (76.8 mg, 0.8 mmol) and toluene (2 mL) was added, and the mixture was stirred at room temperature for 3h. The reaction mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (2×5 mL). The combined organic phase was filtered through a Na_2SO_4 plug, then directly loaded on a silica gel column and purified by column chromatography (silica gel, twice, 0-65 % EtOAc in Hexanes then 0-60% EtOAc in Hexanes) to give the compound **TX63822** as a white solid (22.2 mg, 22%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.22 (s, 1H), 6.03 (s, 1H), 3.25-3.30 (m, 1H), 3.06 (d, 1H, J = 4.5 Hz), 2.56 (s, 3H), 2.42-2.51 (m, 1H), 2.19 (s, 3H), 1.95-2.16 (m, 3H), 1.83-1.93 (m, 2H), 1.58-1.77 (m, 4H), 1.15-1.45 (m, 6H), 1.44 (s, 3H), 1.30 (s, 3H), 1.24 (d, 3H, J = 6.5 Hz), 1.06 (s, 3H), 1.04 (s, 3H), 0.95 (s, 3H); m/z 556 (M+1).

Compound TX64005: Compound **11** (0.3 mmol) and methyl 4-imidazolecarboxylate (185 mg, 1.5 mmol) were taken up in CH_2Cl_2 (5 mL), and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic phase was washed by NaCl (Sat.), dried over Na_2SO_4, then directly loaded on a silica gel column and purified by column chromatography (silica gel, 0-70 % EtOAc in Hexanes) to give the compound **TX64005** as a white solid (52.6 mg, 30%) (only the pure fractions were collected, purification was not optimized). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.26 (s, 1H), 8.02 (s, 1H), 6.05 (s, 1H), 3.94 (s, 3H), 3.23 (d, 1H, J = 4.5 Hz), 3.15-3.22 (m, 1H), 2.43-2.52 (m, 1H), 2.23-2.32 (m, 1H), 1.83-2.05 (m, 4H), 1.56-1.79 (m, 4H), 1.15-1.52 (m, 6H), 1.45 (s, 3H), 1.28 (s, 3H), 1.24 (d, 3H, J = 6.5 Hz), 1.06 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H); m/z 586 (M+1).

Compound TX64006: Compound **11** (0.3 mmol) and hydroxylamine hydrochloride (62.6 mg, 0.9 mmol) were taken up in THF (4.5 mL). Et_3N (0.5 mL) and H_2O (0.3 mL) were added and the mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with HCl (15 mL) and extracted with EtOAc (2×15 mL). The combined organic phase was washed by NaCl (Sat.), dried over Na_2SO_4 and concentrated under reduced pressure to afforded a solid residue, which was purified by column chromatography (silica gel, 0-50% EtOAc in Hexanes) to

give the compound **TX64006** as a white solid (44.4 mg, 30%) (only the pure fractions were collected, purification was not optimized). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, br, 1H), 8.04 (s, 1H), 7.85 (s, br, 1H), 6.12 (s, 1H), 3.01 (d, 1H, *J* = 4.5 Hz), 2.86-2.97 (m, 1H), 2.42-2.52 (m, 1H), 1.95-2.06 (m, 1H), 1.80-1.92 (m, 2H), 1.15-1.79 (m, 12H), 1.43 (s, 3H), 1.33 (s, 3H), 1.25 (d, 3H, *J* = 6.5 Hz), 1.02 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H); m/z 493 (M+1).

Compound TX64007: Compound **11** (0.3 mmol) and 2-oxa-6-azaspiro[3,3]heptanes oxalate (124.7 mg, 0.66 mmol) were taken up in CH_2Cl_2 (5 mL). Et_3N (418 μL, 3 mmol) was added and the mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with HCl (5 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic phase was washed by NaCl (Sat.), dried over Na_2SO_4, then directly loaded on a silica gel column and purified by column chromatography (silica gel, 0-75% EtOAc in Hexanes) to give the compound **TX64007** as a white foam (56.8 mg, 34%) (only the pure fractions were collected, purification was not optimized). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.01 (s, 1H), 4.79 (s, 4H), 4.33 (s, br, 4H), 2.90-3.01 (m, 2H), 2.41-2.51 (m, 1H), 1.83-1.96 (m, 2H), 1.13-1.82 (m, 13H), 1.44 (s, 3H), 1.32 (s, 3H), 1.25 (d, 3H, *J* = 6.4 Hz), 1.01 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); m/z 559 (M+1).

General method A: Compound **11** (~0.2 mmol) and substituted amine (See Table 2 for the amount) were taken up in toluene (2 mL), and the mixture was stirred at room temperature for 1 min. NaOH (10%, 1 mL) was added and the mixture was stirred at room temperature (See Table 2 for the reaction time). The reaction mixture was quenched with HCl (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic phase was washed with NaCl (Sat.), dried over Na_2SO_4, then directly loaded on a silica gel column and purified by column chromatography (silica gel, 0-30% EtOAc in Hexanes) to give the corresponding derivatives:

Compound TX63823: white solid (59.1 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.00 (s, 1H), 3.57 (s, br, 4H), 3.19-3.22 (m, 1H), 3.15 (d, 1H, *J* = 3.5 Hz), 2.44-2.51 (m, 1H), 1.52-2.03 (m, 14H), 1.14-1.52 (m, 5H), 1.44 (s, 3H), 1.32 (s, 3H), 1.25 (d, 3H, *J* = 7.0 Hz), 1.03 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); m/z 531 (M+1).

Compound TX63880: white foam (63.3 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.99 (s, 1H), 3.62 (s, br, 4H), 3.29-3.45 (m, 1H), 3.09-3.13 (m,

1H), 2.41-2.51 (m, 1H), 1.95-2.05 (m, 1H), 1.14-1.92 (m, 20H), 1.44 (s, 3H), 1.33 (s, 3H), 1.25 (d, 3H, J = 6.5 Hz), 1.03 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); m/z 545 (M+1).

Compound TX63881: white foam (60.4 mg, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.00 (s, 1H), 3.59-3.79 (m, 8H), 3.38 (s, br, 1H), 3.05-3.15 (m, 1H), 2.42-2.51 (m, 1H), 1.97-2.07 (m, 1H), 1.82-1.91 (m, 2H), 1.15-1.52 (m, 12H), 1.44 (s, 3H), 1.32 (s, 3H), 1.25 (d, 3H, J = 6.5 Hz), 1.03 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); m/z 547 (M+1).

General method B: Compound **11** (~0.2 mmol) and substituted amine (See Table 2 for the amount) were taken up in CH_2Cl_2 (2 mL). Et_3N (0.5 mL) was added and the mixture was stirred at room temperature (See Table 2 for the reaction time). The reaction mixture was quenched with HCl (5 mL) and extracted with CH_2Cl_2 (10 mL). The organic phase was washed by NaCl (Sat.), dried over Na_2SO_4, then directly loaded on a silica gel column and purified by column chromatography (silica gel, EtOAc in Hexanes) to give the corresponding derivatives:

Compound TX63824: white solid (9.9 mg, 10%); (silica gel, 0-30% EtOAc in Hexanes; only the pure fractions were collected, purification was not optimized). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.03 (s, 1H), 5.75-5.81 (m, 1H), 3.06 (d, 1H, J = 4.5 Hz), 2.75-2.89 (m, 4H), 2.45-2.52 (m, 1H), 1.53-2.01 (m, 8H), 1.40-1.52 (m, 2H), 1.44 (s, 3H), 1.13-1.40 (m, 5H), 1.33 (s, 3H), 1.25 (d, 3H, J = 7.0 Hz), 1.02 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H); m/z 491 (M+1).

Compound TX63882: white foam (8.3 mg, 8.2%); (silica gel, twice, 0-15% EtOAc in Hexanes, then 0-35% EtOAc in Hexanes; only the pure fractions were collected, purification was not optimized). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.02 (s, 1H), 6.04 (s, 1H), 3.76 (s, 3H), 3.11 (d, 1H, J = 4.0 Hz), 2.80-2.87 (m, 1H), 2.43-2.51 (m, 1H), 1.95-2.04 (m, 1H), 1.15-1.92 (m, 14H), 1.45 (s, 3H), 1.37 (s, 3H), 1.26 (d, 3H, J = 7.0 Hz), 1.02 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H); m/z 507 (M+1).

Compound TX63825: white solid (29.0 mg, 27%) (silica gel, 0-20% EtOAc in Hexanes; only the pure fractions were collected, purification was not optimized). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.16 (s, br, 1H), 6.03 (s, 1H), 4.90-5.00 (m, 3H), 4.40-4.52 (m, 2H), 3.06 (d, 1H, J = 4.5 Hz), 2.87-2.93 (m, 1H), 2.44-2.52 (m, 1H), 1.98-2.07 (m, 1H), 1.15-1.93 (m, 14H), 1.45 (s, 3H), 1.33 (s, 3H), 1.25 (d, 3H, J = 6.5 Hz), 1.03 (s, 3H), 1.01 (s, 3H), 0.92 (s, 3H); m/z 533 (M+1).

General method C: Compound **11** (~0.2 mmol) and substituted amine (See Table 2 for the amount) were taken up in toluene (2 mL) and the mixture was stirred

at 80 °C (See Table 2 for the reaction time). The reaction mixture was quenched with HCl (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic phase was washed NaCl (Sat.), dried over Na_2SO_4, then directly loaded on a silica gel column and purified by column chromatography (silica gel, EtOAc in Hexanes) to give the corresponding derivatives:

Compound TX63878: white foam (64.1 mg, 63.5%); (silica gel, 0-15% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.99 (s, 1H), 3.18-3.30 (m, 2H), 3.08 (s, 6H), 2.43-2.50 (m, 1H), 1.96-2.05 (m, 1H), 1.15-1.91 (m, 14H), 1.44 (s, 3H), 1.32 (s, 3H), 1.25 (d, 3H, *J* = 6.5 Hz), 1.02 (s, 6H), 0.91 (s, 3H); m/z 505 (M+1).

Compound TX63877: very light yellow solid (48.6 mg, 45.6%); (silica gel, 0-15% EtOAc in Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.02 (s, 1H), 5.76 (t, 1H, *J* = 5.0 Hz), 3.20-3.33 (m, 2H), 3.07 (d, 1H, *J* = 4.5 Hz), 2.83-2.90 (m, 1H), 2.43-2.52 (m, 1H), 1.85-2.01 (m, 2H), 1.15-1.84 (m, 17H), 1.47 (s, 3H), 1.33 (s, 3H), 1.25 (d, 3H, *J* = 7.0 Hz), 1.02 (s, 3H), 1.00 (s, 3H), 0.92 (t, 3H, *J* = 7.5 Hz), 0.91 (s, 3H); m/z 533 (M+1).

Compound 11: DMF (5 drops) was added to a 0 °C solution of **TX63520** (771 mg, 1.61 mmol) and $(COCl)_2$ (0.41 mL, 4.8 mmol) in CH_2Cl_2 (16 mL) and stirred at 0 °C for 15 min, then warmed to room temperature for 4 h. The resultant solution was concentrated to a yellow foam, azeotroped with CH_2Cl_2 (15 mL), and dried under vacuum to give **11** as a yellow foam. The yellow foam was dissolved in CH_2Cl_2 (16 mL) to give a stock solution (~0.1 M) that was used in subsequent reactions.

Compound TX63784: Methoxyacetic acid hydrazide (67.2 mg, 0.645 mmol) and TEA (0.21 mL, 1.5 mmol) were added to stock **11** (0.1 M in CH_2Cl_2, 3.7 mL, 0.37 mmol), and the mixture stirred at room temperature for 23 h. The resultant solution was diluted with EtOAc (70 mL), washed with 1 M HCl (25 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **TX63784** (151 mg, 72 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, 1H, *J* = 3.5 Hz), 8.02 (s, 1H), 7.90 (d, 1H, *J* = 4.0 Hz), 6.02 (s, 1H), 4.04 (s, 2H), 3.46 (s, 3H), 3.18 (d, 1H, *J* = 4.4 Hz), 3.03 (m, 1H), 2.47 (qd, 1H, *J* = 6.7, 12.8 Hz), 1.99 (m, 4H),

1.63 (m, 7H), 1.44 (s, 3H), 1.39 (s, 3H), 1.33 (m, 4H), 1.25 (d, J = 6.5 Hz, 3H), 1.03 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); m/z 564.3 (M+1).

Compound TX63790: A mixture of **TX63784** (136 mg, 0.241 mmol), TsOH•H_2O (43.4 mg, 0.228 mmol) and PhMe (12 mL) was heated to vigorous reflux with Dean-Stark removal of water for 1 h. The resultant mixture was cooled to room temperature, diluted with EtOAc (30 mL), washed with sat. $NaHCO_3$ (15 mL) and brine (15 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 70 % EtOAc in Hexanes) to give **TX63790** (67.0 mg, 51 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.01 (s, 1H), 4.63 (s, 2H), 3.43 (s, 3H), 3.19 (m, 1H), 3.03 (d, 1H, J = 4.6 Hz), 2.46 (qd, 1H, J = 6.6, 12.8 Hz), 2.21 (dt, 1H, J = 4.0, 13.2 Hz), 1.91 (m, 4H), 1.65 (m, 5H), 1.41 (s, 3H), 1.35 (m, 5H), 1.24 (d, 3H, J = 6.6 Hz), 1.16 (s, 3H), 1.06 (s, 6H), 0.95 (s, 3H); m/z 546.3 (M+1).

Compound TX63785: Formic acid hydrazide (55.9 mg, 0.931 mmol) and TEA (0.26 mL, 1.9 mmol) were added to stock **11** (0.1 M in CH_2Cl_2, 4.6 mL, 0.46 mmol), and the mixture stirred at room temperature for 23 h. The resultant solution was diluted with EtOAc (70 mL), washed with 1 M HCl (25 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **TX63785** (112 mg, 47 %) as a white solid: ^{1}H NMR (500MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.10 (d, 1H, J = 4.0 Hz), 8.02 (s, 1H), 7.90 (d, 1H, J = 4.0 Hz), 6.03 (s, 1H), 3.17 (d, 1H, J = 4.0 Hz), 3.02 (m, 1H), 2.47 (qd, 1H, J = 6.8, 12.6 Hz), 2.09 (m, 1H), 1.89 (m, 3H), 1.64 (m, 8 H), 1.44 (s, 3H), 1.37 (s, 3H), 1.32 (m, 3H), 1.25 (d, 3H, J = 6.7 Hz), 1.03 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); m/z 520.3 (M+1).

Compound TX63789: A mixture of **TX63785** (94 mg, 0.181 mmol), TsOH•H_2O (34.4 mg, 0.181 mmol) and PhMe (12 mL) was heated to vigorous reflux with Dean-Stark removal of water for 45 min. The resultant mixture was cooled to room temperature, diluted with EtOAc (50 mL), washed with sat. $NaHCO_3$ (25 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 75 % EtOAc in Hexanes) to give **TX63789** (31.0 mg, 34 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.00 (s, 1H), 6.01 (s, 1H), 3.20 (m, 1H), 2.93 (d, 1H, J = 3.2 Hz), 2.46 (qd, 1H, J = 6.2, 12.4 Hz), 2.22 (dt, 1H, J = 3.9, 14.1 Hz), 1.91 (m, 4H), 1.64 (m, 5H), 1.41 (s,

3H), 1.32 (m, 5H), 1.24 (d, 3H, J = 6.5 Hz), 1.15 (s, 3H), 1.06 (s, 6H), 0.95 (s, 3H); m/z 502.3 (M+1).

Compound TX63786: Acetamide oxime (34.4 mg, 0.464 mmol) and TEA (0.14 mL, 1.00 mmol) were added to stock **11** (0.1 M in CH_2Cl_2, 2.5 mL, 0.25 mmol), and the mixture stirred at room temperature for 23 h. The resultant solution was concentrated and the crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **TX63786** (82 mg, 61 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.02 (s, 1H), 4.68 (br s, 2H), 3.10 (m, 1H), 3.06 (d, 1H, J = 4.5 Hz), 2.47 (qd, 1H, J = 6.7, 12.6 Hz), 1.98 (s, 3H), 1.81 (m, 7H), 1.51 (m, 2H), 1.44 (s, 3H), 1.34 (s, 3H), 1.29 (m, 6H), 1.24 (d, 3H, J = 6.9 Hz), 1.02 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H); m/z 534.3 (M+1).

Compound TX63787: A solution of **TX63786** (74 mg, 1 mmol) in EtOAc (0.15 mL) and PhMe (1.35 mL) were sealed in a microwave vial and heated to 200 °C for 20 min. The solution was concentrated and the crude residue was purified by column chromatography (silica gel, 0 → 55 % EtOAc in Hexanes) to give **TX63787** (17.2 mg, 24 %) as an off-white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.02 (s, 1H), 3.25 (m, 1H), 3.05 (d, 1H, J = 4.6 Hz), 2.46 (qd, 1H, J = 6.5, 12.8 Hz), 2.38 (s, 3H), 2.20 (dt, 1H, J = 4.0, 14.0 Hz), 1.90 (m, 3H), 1.65 (m, 7H), 1.41 (s, 3H), 1.33 (m, 4H), 1.23 (d, 3H, J = 8.0 Hz), 1.12 (s, 3H), 1.05 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H); m/z 516.3 (M+1).

Compound 62: A mixture of methyl magnesium carbonate (2.0 M in DMF, 2.25 mL, 4.50 mmol) and **7** (238 mg, 0.508 mmol) was heated to 110 °C with a constant N_2 sparge for 1.5 h. The resultant solution was cooled to room temperature, diluted with EtOAc (75 mL), washed with 1M HCl (50 mL) and brine (25 mL), dried with Na_2SO_4 and concentrated to give **62** (257 mg, 99 %) as an off-white solid: m/z 513.3 (M+1).

Compound 63: $TMSCHN_2$ (2.0 M in THF, 0.51 mL, 1.02 mmol) was added to a 0 °C solution of **62** (257 mg, 0.501 mmol) in THF (8.0 mL) and MeOH (2.0 mL). The resultant solution was stirred for 1.5 h at 0 °C, diluted with EtOAc (150 mL), washed with sat. $NaHCO_3$ (50 mL) and brine (25 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 45 % EtOAc in Hexanes) to give **63** as a glassy solid that was used as-is in next reaction: m/z 527.4 (M+1).

Compound TX63788: Pyridine (77 uL, 0.95 mmol) was added to a 0 °C solution of PhSeCl (168 mg, 0.876 mmol) in CH_2Cl_2 (3 mL). After 15 min a solution of **63** (228 mg, 0.433 mmol) in CH_2Cl_2 (8.7 mL) was added and the reaction stirred at 0 °C for 1.5 h. The resultant solution was diluted with CH_2Cl_2 (10 mL), washed with 1M HCl (2 × 5 mL), cooled to 0 °C, and H_2O_2 (30 %, 0.42 mL) added. The biphasic mixture was vigorously stirred for 1 h, then diluted with CH_2Cl_2 (50 mL), washed with 10% Na_2SO_3 (25 mL) and brine (25 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 50 % EtOAc in Hexanes) to give **TX63788** (175 mg, 67 % from **63**) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.12 (s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.05 (m, 1H), 2.94 (d, 1H, *J* = 4.0 Hz), 2.42 (qd, 1H, *J* = 6.5, 11.8 Hz), 1.87 (m, 3H), 1.59 (m, 8H), 1.39 (s, 3H), 1.32 (s, 3H), 1.25 (m, 4H), 1.22 (d, 3H, *J* = 6.4 Hz), 1.01 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H); m/z 525.3 (M+1).

Compound TX63830: A suspension of **TX63788** (353 mg, 0.673 mmol), KOH (1.89 g, 33.7 mmol), H_2O (7 mL), and MeOH (21 mL) was heated to reflux for 10 min. The resultant solution was cooled to room temperature, diluted with EtOAc (75 mL), washed with 1 M HCl (50 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 60 % EtOAc in Hexanes each containing 0.5% HOAc) to give **TX63830** (210 mg, 61 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.50 (br s, 1H), 8.77 (s, 1H), 6.22 (s, 1H), 3.69 (s, 3H), 3.05 (m, 1H), 2.93 (d, 1H, *J* = 4.7 Hz), 2.60 (qd, 1H, *J* = 6.7, 12.7 Hz), 1.79 (m, 7H), 1.53 (m, 4H), 1.44 (s, 3H), 1.34 (s, 3H), 1.26 (d, 3H, *J* = 6.6 Hz), 1.25 (m, 4H), 1.00 (s, 6H), 0.89 (s, 3H); m/z 511.4 (M+1).

Compound TX63831: A mixture of **TX63788** (100.6 mg, 0.192 mmol) and NH_3 (2.0 M in MeOH, 9.5 mL, 19 mmol) was stirred at room temperature for 12 d. The resultant solution was concentrated and purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **TX63831** (39 mg, 40 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.44 (br s, 1H), 6.27 (s, 1H), 5.62 (br s, 1H), 3.69 (s, 3H), 3.05 (m, 1H), 2.91 (d, 1H, *J* = 4.6 Hz), 2.49 (qd, 1H, *J* = 6.7, 12.2 Hz), 1.87 (m, 3H), 1.69 (m, 5H), 1.50 (m, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.26 (m, 4H), 1.23 (d, 3H, *J* = 6.7 Hz), 1.00 (s, 6H), 0.89 (s, 3H); m/z 510.3 (M+1).

Compound TX63716: EDCI (192 mg, 1.00 mmol) was added to a room temperature solution of **TX63545** (286 mg, 0.617 mmol), *N*-Boc-Gly-OH (165 mg,

0.942 mmol), DMAP (20.7 mg, 0.169 mmol), and CH_2Cl_2 (12.4 mL) and the mixture stirred at room temperature for 19 h. The resultant solution was diluted with EtOAc (100 mL), washed with 1 M HCl (25 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 75 % EtOAc in Hexanes) to give **TX63716** (326 mg, 85 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 5.00 (br s, 1H), 4.14 (m, 2H), 3.95 (m, 2H), 2.98 (d, 1H, *J* = 3.5 Hz), 2.48 (qd, 1H, *J* = 6.0, 12.6 Hz), 2.35 (br d, 1H, *J* = 12.5 Hz), 1.89 (m, 2H), 1.73 (m, 4H), 1.49 (m, 2H), 1.45 (s, 9H), 1.48 (s, 3H), 1.46 (s, 3H), 1.27 (m, 5H), 1.26 (d, 3H, *J* = 6.8 Hz), 1.12 (m, 2H), 1.02 (s, 3H), 0.94 (s, 3H), 0.88 (s, 3H); m/z 565.3 (M-55) (M-C_4H_8+H).

Compound TX63717: HCl (4.0 M in 1,4-dioxane, 0.94 mL, 3.76 mmol) was added to a room temperature solution of **TX63716** (293 mg, 0.472 mmol) in CH_2Cl_2 (10 mL). After 6 h the solution was diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 50 → 100 % EtOAc in Hexanes, each with 0.5% TEA) to give **TX63717** (209 mg, 85 %) as a pale-yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.04 (s, 1H), 4.18 (d, 1H, *J* = 11.0 Hz), 4.09 (d, 1H, *J* = 11.3 Hz), 3.48 (s, 2H), 3.01 (d, 1H, *J* = 4.6 Hz), 2.49 (qd, 1H, *J* = 6.6, 12.7 Hz), 2.37 (m, 1H), 1.92 (m, 2H), 1.63 (m, 7H), 1.50 (s, 3H), 1.47 (s, 3H), 1.27 (d, 3H, *J* = 6.6 Hz), 1.26 (m, 5H), 1.09 (m, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.89 (s, 3H); m/z 521.3 (M+1).

Compound TX63832: PhSeCl (334 mg, 1.74 mmol) was added to a room temperature suspension of **7** (469 mg, 1.00 mmol) in EtOAc (20 mL). After 6 h the resultant solution was washed with water (2 × 25 mL), and the mixture stored at -20 °C overnight. The solution was warmed to room temperature and THF (8 mL) and H_2O_2 (30 %, 1.0 mL) were added. The mixture was stirred at room temperature for 1 h, diluted with EtOAc (50 mL), washed with 10% Na_2SO_3 (25 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 30 % EtOAc in Hexanes) to give **TX63832** (255 mg, 55 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, 1H, *J* = 10.4 Hz), 6.05 (s, 1H), 5.89 (d, 1H, *J* = 10.3 Hz), 3.69 (s, 3H), 3.05 (m, 1H), 2.92 (d, 1H, *J* = 4.6 Hz), 2.38 (qd, 1H, *J* = 5.8, 12.5 Hz), 1.87 (m, 3H), 1.57 (m, 8H), 1.36 (s, 3H), 1.31 (s,

3H), 1.27 (m, 4H), 1.19 (d, 3H, J = 6.7 Hz), 1.01 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H);m/z 467.4 (M+1).

Compound TX63833: A solution of **TX63832** (231 mg, 0.495 mmol), I_2 (251 mg, 0.989 mmol), pyridine (0.12 mL, 1.48 mmol), and THF (10 mL) was heated to reflux for 17 h. The resultant mixture was cooled to room temperature; diluted with EtOAc (100 mL); washed with sat. $Na_2S_2O_3$ (40 mL), 1 M HCl (50 mL), and sat. $NaHCO_3$ (25 mL); dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 30 % EtOAc in Hexanes) to give **TX63833** (175 mg, 60 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 6.04 (s, 1H), 3.69 (s, 3H), 3.05 (m, 1H), 2.93 (d, 1H, J = 4.5 Hz), 2.55 (qd, 1H, J = 6.1, 12.6 Hz), 1.69 (m, 11H), 1.38 (s, 3H), 1.30 (s, 3H), 1.27 (m, 4H), 1.26 (d, 3H, J = 6.7 Hz), 1.02 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H); m/z 593.2 (M+1).

Compound 64: LAH (2.0 M in THF, 32 mL, 64 mmol) was added to a 0 °C solution of **7** (6.06 g, 12.9 mmol) in THF (225 mL). The mixture was stirred at 0 °C for 1 h; warmed to room temperature for 26 h; cooled to 0 °C; quenched by the successive addition of water (2.4 mL), 4 M NaOH (2.4 mL, and water (2.4 mL); warmed to room temperature; diluted with MTBE (100 mL); stirred for 1 h; filtered through celite; eluted with CH_2Cl_2 (100 mL) and concentrated to give **64** (5.79 g, quantitative) as a white foam that was used without further purification: m/z 427.3 (M-17), (M-H_2O+H).

Compound 65: A biphasic solution of **64** (all above obtained, ~12.9 mmol), $PhI(OAc)_2$ (9.35 g, 29.0 mmol), TEMPO (2.01 g, 12.9 mmol), water (13 mL), and CH_2Cl_2 (1.3 L) was stirred vigorously at room temperature for 21 h. The resultant mixture was dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **65** (1.56 g, 27 %) as a white solid: m/z 425.3 (M-17), (M-H_2O+H).

Compound 66: Triethyl phosphonoacetate (3.52 mL, 17.7 mmol) was added to a 0 °C suspension of NaH (60%, 712 mg, 17.8 mmol) in THF (53 mL) and warmed to room temperature over 15 min. The resultant solution was cooled to 0 °C and a solution of **65** (1.56 g, 3.52 mmol) in THF (17.5 mL) was added and the transfer completed with THF (5 mL). The mixture was warmed to room temperature and stirred for 17.5 h, quenched by the addition of water (50 mL) and 1 M HCl (25 mL), and extracted with CH_2Cl_2 (300 mL, then 100 mL). The combined organic fractions

were washed with sat. $NaHCO_3$ (100 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **66** (1.212 g, 67 %) as a white solid: m/z 495.3 (M-17), (M-H_2O+H).

Compound 67: TPAP (82 mg, 0.233 mmol) was added to a room temperature solution of **66** (1.212 g, 2.364 mmol), NMO (831 mg, 7.09 mmol) and 4 Å molecular sieves (3.04 g) in CH_2Cl_2 (50 mL). The resultant mixture was stirred at room temperature for 1.5 h, concentrated to ~3 mL, and purified by column chromatography (silica gel, 0 → 65 % EtOAc in Hexanes) to give **67** (1.057 g, 88 %) as a white solid: m/z 509.3 (M+1).

Compound 68: A flask containing a room temperature suspension of **67** (1.057 g, 2.078 mmol) and Pd/C (10 %, 260 mg) in THF (42 mL) was purged with N_2 then H_2. The suspension was stirred under H_2 (balloon) for 17 h, sparged with N_2, filtered through celite, eluted with THF (50 mL), and concentrated to give **68** (1.094 g, quantitative) as a white solid that was used without further purification: m/z 511.3 (M+1).

Compound 69: A solution of **68** (all above obtained, ~2.078 mmol), NaOMe (25 % in MeOH, 5.25 mL) and EtOCHO (15.75 mL) was stirred at room temperature for 3.5 h, diluted with 1 M HCl (50 mL), and extracted with EtOAc (2 × 100 mL). The combined organic fractions were washed with brine (25 mL), dried with Na_2SO_4, and concentrated to give **69** (mixture of Me- and Et-esters ~ 1 : 2.4) as an off-white foam solid that was used without further purification: Me-ester m/z 525.3 (M+1), Et-ester m/z 539.3 (M+1).

Compound 70: A mixture of **69** (all above obtained, ~2.078 mmol), NH_2OH•HCl (192 mg, 2.76 mmol), EtOH (18 mL) and water (3 mL) was heated to 55 °C for 17 h. The resultant solution was cooled to room temperature, diluted with 1 M HCl (50 mL) and extracted with EtOAc (100 mL, then 75 mL). The combined organic fractions were dried with Na_2SO_4 and concentrated. The resultant residue was dissolved in MeOH (100 mL), treated with 12 M HCl (0.25 mL), and stirred at room temperature for 3 h. The mixture was diluted with 1 M HCl (50 mL) and extracted with EtOAc (2 × 100 mL). The combined organic fractions were washed with brine (50 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 60 % EtOAc in Hexanes) to give

70 (876 mg, Me- : Et-ester = 41 : 57, 80 % from **68**) as a white solid: Me-ester m/z 522.3 (M+1), Et-ester m/z 536.3 (M+1).

Compound 71: A solution of **70** (876 mg, Me- : Et-ester = 41 : 57, 1.65 mmol), NaOMe (1.0 mL, 25% in MeOH), and MeOH (21 mL) was heated to 55 °C for 2 h. The resultant mixture was diluted 1 M HCl (50 mL) and extracted with EtOAc (100 mL, then 2 × 50 mL). The combined organic fractions were washed with brine (25 mL), dried with Na_2SO_4, and concentrated to give **71** (900 mg, quantitative) as a white foam solid that was used without further purification: m/z 522.3 (M+1).

Compound TX63867: DBDMH (236.5 mg, 0.827 mmol) was added to a 0 °C solution of **71** (all above obtained, ~1.65 mmol) in DMF (20 mL). The mixture was stirred at 0 °C for 2.5 h, pyridine (0.53 mL, 6.6 mmol) added, and the reaction heated to 55 °C for 16 h. The reaction was cooled to room temperature; diluted with EtOAc (200 mL); washed with 1 M HCl (25 mL), 10 % Na_2SO_3 (25 mL) and brine (25 mL); dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 75 % EtOAc in Hexanes) to give **TX63867** (708 mg, 82 %) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 3.67 (s, 3H), 3.07 (d, 1H, *J* = 4.6 Hz), 2.48 (qd, 1H, *J* = 6.7, 12.3 Hz), 2.30 (m, 3H), 1.68 (m, 11H), 1.51 (s, 3H), 1.46 (s, 3H), 1.26 (d, 3H, *J* = 6.7 Hz), 1.25 (m, 4H), 1.04 (m, 2H), 1.02 (s, 3H), 0.93 (s, 3H), 0.88 (s, 3H); m/z 520.3 (M+1).

Compound TX63891: A suspension of **TX63867** (643 mg, 1.24 mmol) in MeCN (37.5 mL) and 1 M HCl (12.5 mL) was heated to 65 °C overnight. The resultant solution was cooled to room temperature, diluted with 1 M HCl (50 mL) and extracted with EtOAc (150 mL, then 100 mL). The combined organic fractions were washed with brine (50 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes both containing 0.5 % HOAc), like fractions were combined, concentrated, azeotroped with PhMe (100 mL) then EtOH (50 mL), and dried to give **TX63891** (583 mg, 93 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (br s, 1H), 8.03 (s, 1H), 6.04 (s, 1H), 3.08 (d, 1H, *J* = 4.5 Hz), 2.48 (qd, 1H, *J* = 6.7, 12.6 Hz), 2.32 (m, 3H), 1.69 (m, 11H), 1.49 (s, 3H), 1.46 (s, 3H), 1.27 (m, 4H), 1.26 (d, 3H, *J* = 6.8 Hz), 1.04 (m, 2H), 1.01 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H); m/z 506.3 (M+1).

Compound TX63886: EDCI (39.3 mg, 0.205 mmol) was added to a solution of **TX63891** (50.5 mg, 0.0999 mmol), $MeNH_2$•HCl (16.3 mg, 0.241 mmol), TEA (28

uL, 0.20 mmol) and DMAP (25.8 mg, 0.211 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 18 h. The resultant solution was diluted with EtOAc (25 mL), washed with 1 M HCl (15 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63886** (39.3 mg, 76 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.02 (s, 1H), 5.44 (br s, 1H), 3.10 (d, 1H, *J* = 3.9 Hz), 2.80 (d, 3H, *J* = 4.5 Hz), 2.48 (qd, 1H, *J* = 6.5, 12.4 Hz), 2.23 (m, 1H), 2.13 (m, 2H), 1.88 (m, 4H), 1.59 (m, 7H), 1.53 (s, 3H), 1.46 (s, 3H), 1.26 (d, 3H, *J* = 6.9 Hz), 1.25 (m, 4H), 1.02 (m, 2H), 1.00 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H); m/z 519.3 (M+1).

Compound TX63892: EDCI (39.0 mg, 0.203 mmol) was added to a solution of **TX63891** (50.3 mg, 0.0995 mmol), $EtNH_2$•HCl (18.5 mg, 0.227 mmol), TEA (28 uL, 0.20 mmol) and DMAP (24.8 mg, 0.203 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 17 h. The resultant solution was diluted with EtOAc (25 mL), washed with 1 M HCl (15 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63892** (44.9 mg, 85 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.02 (s, 1H), 5.41 (br s, 1H), 3.28 (dq, 2H, *J* = 6.6, 7.0 Hz), 3.11 (d, 1H, *J* = 4.2 Hz), 2.48 (qd, 1H, *J* = 6.5, 12.5 Hz), 2.23 (m, 1H), 2.12 (t, 2H, *J* = 8.0 Hz), 1.89 (m, 4H), 1.60 (m, 7H), 1.53 (s, 3H), 1.46 (s, 3H), 1.26 (d, 3H, *J* = 6.8 Hz), 1.23 (m, 4H), 1.13 (t, 3H, *J* = 7.3 Hz), 1.02 (m, 2H), 1.00 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H); m/z 533.4 (M+1).

Compound TX63887: EDCI (39.0 mg, 0.203 mmol) was added to a solution of **TX63891** (50.6 mg, 0.100 mmol), 2,2,2-trifluoroethylamine hydrochloride (27.7 mg, 0.204 mmol), TEA (28 uL, 0.20 mmol) and DMAP (25.0 mg, 0.205 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 18 h. The resultant solution was diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63887** (45.0 mg, 77 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.03 (s, 1H), 5.70

(br s, 1H), 3.98 (m, 1H), 3.86 (m, 1H), 3.08 (d, 1H, J = 4.1 Hz), 2.48 (qd, 1H, J = 6.5, 11.9 Hz), 2.22 (m, 3H), 1.78 (m, 8H), 1.51 (s, 3H), 1.48 (m, 3H), 1.46 (s, 3H), 1.26 (d, 3H, J = 6.6 Hz), 1.25 (m, 4H), 1.02 (m, 2H), 1.01 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H); m/z 587.3 (M+1).

Compound TX63888: EDCI (38.5 mg, 0.201 mmol) was added to a solution of **TX63891** (49.8 mg, 0.0985 mmol), morpholine (18 uL, 0.207 mmol), TEA (28 uL, 0.20 mmol) and DMAP (24.5 mg, 0.201 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 18 h. The resultant solution was diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63888** (38.9 mg, 69 %) as a white solid: ^{1}H NMR (500x MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.02 (s, 1H), 3.64 (m, 6H), 3.48 (m, 2H), 3.10 (d, 1H, J = 3.8 Hz), 2.48 (qd, 1H, J = 6.2, 12.9 Hz), 2.33 (m, 1H), 2.23 (m, 2H), 1.77 (m, 8H), 1.50 (s, 3H), 1.50 (m, 3H), 1.45 (s, 3H), 1.26 (d, 3H, J = 6.2 Hz), 1.25 (m, 4H), 1.04 (m, 2H), 1.01 (s, 3H), 0.93 (s, 3H), 0.88 (s, 3H); m/z 575.4 (M+1).

Compound TX63889: EDCI (39.0 mg, 0.203 mmol) was added to a solution of **TX63891** (50.2 mg, 0.0993 mmol), azetidine hydrochloride (19.0 mg, 0.203 mmol), TEA (28 uL, 0.20 mmol) and DMAP (25.0 mg, 0.205 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 18 h. The resultant solution was diluted with EtOAc (25 mL), washed with 1 M HCl (15 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63889** (45.6 mg, 84 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.01 (s, 1H), 4.16 (m, 2H), 4.00 (t, 2H, J = 7.6 Hz), 3.12 (d, 1H, J = 7.6 Hz), 2.48 (d, 1H, J = 6.6, 12.5 Hz), 2.25 (m, 3H), 1.75 (m, 13H), 1.52 (s, 3H), 1.46 (s, 3H), 1.25 (d, 3H, J = 6.7 Hz), 1.24 (m, 4H), 1.00 (s, 3H), 0.97 (m, 2H), 0.93 (s, 3H), 0.87 (s, 3H); m/z 545.3 (M+1).

Compound TX63893: EDCI (39.3 mg, 0.205 mmol) was added to a solution of **TX63891** (51.3 mg, 0.101 mmol), pyrrolidine (17 uL, 0.206 mmol), TEA (28 uL, 0.20 mmol) and DMAP (25.3 mg, 0.207 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 17 h. The resultant solution was diluted with EtOAc (25 mL), washed with 1 M HCl (15 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. The

crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63893** (41.5 mg, 74 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.01 (s, 1H), 3.44 (t, 4H, *J* = 6.7 Hz), 3.14 (d, 1H, *J* = 4.3 Hz), 2.48 (qd, 1H, *J* = 6.5, 12.4 Hz), 2.22 (m, 3H), 1.91 (m, 7H), 1.60 (m, 7H), 1.53 (s, 3H), 1.45 (s, 3H), 1.25 (d, 3H, *J* = 6.6 Hz), 1.24 (m, 5H), 1.02 (m, 2H), 1.01 (s, 3H), 0.93 (s, 3H), 0.87 (s, 3H); m/z 559.4 (M+1).

Compound TX63890: EDCI (39.7 mg, 0.207 mmol) was added to a solution of **TX63891** (49.9 mg, 0.0987 mmol), 3,3-difluoropyrrolidine hydrochloride (28.6 mg, 0.199 mmol), TEA (28 uL, 0.20 mmol) and DMAP (23.8 mg, 0.195 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 18 h. The resultant solution was diluted with EtOAc (25 mL), washed with 1 M HCl (25 mL) and brine (10 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63890** (46.3 mg, 79 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.02 (s, 1H), 3.75 (m, 4H), 3.11 (d, 1H, *J* = 4.0 Hz), 2.31 (m, 6H), 1.89 (m, 4H), 1.70 (m, 4H), 1.52 (s, 3H), 1.50 (m, 3H), 1.46 (s, 3H), 1.26 (d, 3H, *J* = 6.6 Hz), 1.25 (m, 4H), 1.03 (m, 2H), 1.01 (s, 3H), 0.93 (s, 3H), 0.88 (s, 3H); m/z 595.4 (M+1).

Compound TX63914: EDCI (38.8 mg, 0.202 mmol) was added to a solution of **TX63891** (49.9 mg, 0.0987 mmol), oxetan-3-amine hydrochloride (22.7 mg, 0.207 mmol), TEA (40 uL, 0.29 mmol) and DMAP (25.9 mg, 0.212 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 17 h. The resultant solution was diluted with EtOAc (50 mL), washed with 1 M HCl (20 mL) and brine (15 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63914** (41.4 mg, 75 %) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.00 (s, 1H), 5.93 (d, 1H, *J* = 6.7 Hz), 5.01 (m, 1H), 4.90 (dt, 2H, *J* = 2.6, 6.9 Hz), 4.46 (dt, 2H, *J* = 3.1, 6.5 Hz), 3.06 (d, 1H, *J* = 4.5 Hz), 2.46 (qd, 1H, *J* = 6.7, 12.3 Hz), 2.22 (m, 1H), 2.16 (t, 2H, *J* = 8.3 Hz), 1.67 (m, 10H), 1.49 (s, 3H), 1.44 (s, 3H), 1.24 (d, 3H, *J* = 6.8 Hz), 1.23 (m, 5H), 1.01 (m, 2H), 0.99 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H); m/z 561.3 (M+1).

Compound TX63915: EDCI (59.0 mg, 0.308 mmol) was added to a solution of **TX63891** (76.5 mg, 0.151 mmol), acetic acid hydrazide (22.0 mg, 0.297 mmol), TEA (0.050 mL, 0.36 mmol) and DMAP (37.3 mg, 0.305 mmol) in CH_2Cl_2 (3 mL) and stirred at room temperature for 17 h. The resultant solution was diluted with EtOAc (50 mL), washed with 1 M HCl (20 mL) and brine (15 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 75 % EtOAc in Hexanes) to give **TX63915** (63 mg, 74 %) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.91 (m, 2H), 6.03 (s, 1H), 3.09 (d, 1H, *J* = 4.5 Hz), 2.48 (qd, 1H, *J* = 6.9, 12.7 Hz), 2.06 (s, 3H), 1.64 (m, 14H), 1.52 (s, 3H), 1.46 (s, 3H), 1.26 (d, 3H, *J* = 6.7 Hz), 1.24 (m, 4H), 1.03 (m, 2H), 1.02 (s, 3H), 0.93 (s, 3H), 0.88 (s, 3H); m/z 562.3 (M+1).

Compound TX63916: A mixture of **TX63915** (49 mg, 0.087 mmol), TsOH•H_2O (10 mg, 0.053 mmol) and PhMe (10 mL) was heated to vigorous reflux with Dean-Stark removal of water for 2 h. The resultant mixture was concentrated, and the crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **TX63916** (34.4 mg, 73 %) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.03 (s, 1H), 3.05 (d, 1H, *J* = 4.6 Hz), 2.79 (t, 2H, *J* = 8.4 Hz), 2.49 (s, 3H), 2.48 (qd, 1H, *J* = 6.7, 12.2 Hz), 2.28 (m, 1H), 1.97 (m, 3H), 1.63 (m, 7H), 1.48 (s, 3H), 1.46 (s, 3H), 1.27 (m, 5H), 1.26 (d, 3H, *J* = 6.7 Hz), 1.07 (m, 2H), 1.03 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H); m/z 544.3 (M+1).

Compound 72: DIBAL-H (1.0 M in PhMe, 5.0 mL, 5.0 mmol) was added to a 0 °C solution of **8** (R = Me : Et ~ 30 : 68, 502 mg, 0.94 mmol) in THF (10 mL). The mixture was stirred at 0 °C for 15 min then warmed to room temperature for 2.5 h. The homogeneous solution was cooled to 0 °C, carefully quenched with sat. NaK tartrate (10 mL), diluted with MTBE (25 mL), and stirred at room temperature. The mixture was diluted with water (20 mL) and sat NaK tartrate (20 mL), the organic fraction separated and the aqueous layer extracted with MTBE (25 mL × 2). The combined organic fractions were washed with brine (25 mL), dried with Na_2SO_4 and concentrated to give crude **72** (509 mg, quantitative) as a white foam that was used without further purification: m/z 496.3 (M+1).

Compound 73: NBS (250 mg, 1.40 mmol) was added in one portion to a solution of **72** (above obtained, ~0.94 mmol) in DME/H_2O (9:1, 10 mL) at room temperature, and the flask wrapped in foil. After 2 h 2 % Na_2SO_3 (30 mL) was added

and the mixture stirred at room temperature for 30 min. The resultant mixture was extracted with EtOAc (60 mL), the organic fraction washed with brine (25 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **73** (378 mg, 81 % from **8**) as a white solid: m/z 494.3 (M+1).

Compound 74: A solution of **73** (378 mg, 0.766 mmol), NaOMe (1.05 mL, 25% in MeOH), and MeOH (25 mL) was heated to 55 °C for 1.5 h. The resultant mixture was diluted with EtOAc (175 mL), washed with 1 M HCl (50 mL) and brine (25mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes) to give **74** (254 mg, 67 %) as a white solid: m/z 494.3 (M+1).

Compound TX63918: DBDMH (74.7 mg, 0.261 mmol) was added to a 0 °C solution of **74** (254 mg, 0.514 mmol) in DMF (10 mL). The mixture was stirred at 0 °C for 2.5 h, pyridine (0.17 mL, 2.1 mmol) added, and the reaction heated to 55 °C. The reaction was cooled to room temperature after 4 h and stirred n additional 16 h. The resultant solution was diluted with EtOAc (150 mL), washed with 1 M HCl (50 mL) and brine (25 mL), dried with Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63918** (210 mg, 83 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.03 (s, 1H), 3.68 (m, 3H), 3.07 (d, 1H, J = 4.3 Hz), 2.48 (dq, 1H, J = 6.6, 12.6 Hz), 2.25 (br d, 1H, J = 13.0 Hz), 1.73 (m, 6H), 1.50 (m, 4H), 1.47 (s, 3H), 1.46 (s, 3H), 1.25 (m, 10H), 1.03 (m, 2H), 1.01 (s, 3H), 0.93 (s, 3H), 0.87 (s, 3H); m/z 491.9 (M+1).

Compound TX63920: A solution of **TX63918** (50 mg, 0.10 mmol), Ac_2O (53 uL, 0.56 mmol), pyridine (90 uL, 1.1 mmol) and DMAP (4.0 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 18 h. The resultant solution was diluted with EtOAc (70 mL), washed with 1 M HCl (25 mL) and brine (15 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63920** (50.6 mg, 95 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.03 (s, 1H), 4.05 (m, 2H), 3.04 (d, 1H, J = 3.8 Hz), 2.48 (qd, 1H, J = 6.7, 12.6 Hz), 2.24 (br d, 1H, J =

13.6 Hz), 2.04 (s, 3H), 1.89 (m, 2H), 1.60 (m, 10H), 1.47 (s, 3H), 1.46 (s, 3H), 1.26 (d, 3H, J = 6.5 Hz), 1.24 (m, 5H), 1.05 (m, 2H), 1.01 (s, 3H), 0.93 (s, 3H), 0.87 (s, 3H); m/z 533.9 (M+1).

Compound TX63919: A solution of **TX63918** (49.2 mg, 0.100 mmol), MeOTf (65 uL, 0.57 mmol) and 2,6-^{t}Bu-4-Me-pyridine in CH_2Cl_2 (2 mL) was stirred at room temperature for 18.5 h. The resultant solution was diluted with EtOAc (70 mL), washed with 1 M HCl (20 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63919** (36.8 mg, 73 %) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.02 (s, 1H), 3.36 (m, 2H), 3.32 (s, 3H), 3.08 (d, 1H, J = 4.2 Hz), 2.48 (qd, 1H, J = 6.6, 12.5 Hz), 2.24 (br d, 1H, J = 13.0 Hz), 1.78 (m, 6H), 1.51 (m, 6H), 1.47 (s, 3H), 1.46 (s, 3H), 1.26 (t, 3H, J = 6.5 Hz), 1.24 (m, 5H), 1.03 (m, 2H), 1.00 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H); m/z 505.9 (M+1).

Compound TX63982: A solution of **TX63918** (39.5 mg, 0.0803 mmol) and EtNCO (64 uL, 0.81 mmol) in PhMe (0.5 mL) was stirred at room temperature for 1 h, heated to 70 °C for ~5 h, and stirred at room temperature an additional 19 h. The resultant solution was purified by column chromatography (silica gel, 0 → 100 % EtOAc in Hexanes), like fractions were combined, concentrated, azeotroped with EtOH, and dried to give **TX63982** (33.2 mg, 73 %) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 4.55 (br s, 1H), 4.05 (m, 2H), 3.21 (m, 2H), 3.04 (d, 1H, J = 4.6 Hz), 2.48 (qd, 1H, J = 7.0, 12.3 Hz), 2.26 (td, 1H, J = 4.3, 17.3 Hz), 1.66 (m, 12H), 1.46 (s, 6H), 1.26 (d, 3H, J = 6.7 Hz), 1.25 (m, 5H), 1.13 (t, 3H, J = 7.2 Hz), 1.05 (m, 2H), 1.01 (s, 3H), 0.93 (s, 3H), 0.87 (s, 3H); m/z 563.4 (M+1).

Compound TX63448: Compound **TX63435** (20 mg, 0.041 mmol) and SeO_2 (13.5 mg, 0.12 mmol) were mixed with 1,4-dioxane (1 mL). After heated at 100 °C for 16 h, the reaction mixture was cooled to room temperature, and was filtered through a pad of silica gel, which was eluted with EtOAc. The combined filtrate and washes were concentrated to give the crude product, which contains 12% of **TX63448**. The crude product was repeatedly purified by column chromatography (silica gel, eluting with 0% to 30% EtOAc in hexanes or 0-10% EtOAc in CH_2Cl_2) to compound **TX63448** (1.1 mg) as a white solid: m/z = 490.3 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 5.96 (s, 1H), 3.73 (s, 3H), 3.06 (m, 1H), 2.99 (d, 1H, J =

4.5 Hz), 2.94 (m, 1H), 2.62 (m, 1H), 2.02 (s, 3H), 1.67 (s, 3H), 1.50 (s, 3H), 1.10-1.95 (m, 12H), 1.01 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

Compound TX63936: A solution of compound **TX63520** (370 mg, 0.77 mmol) in CH_2Cl_2 (8 mL) was added to XeF_2 (157 mg, 0.93 mmol) at room temperature in a PTFE tube. After stirred at room temperature for 16 h, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with aq. $NaHCO_3$ solution, and water. The organic extract was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-25% EtOAc in hexanes) to give product **TX63936** (80 mg), which was contaminated with some impurities. The product was purified again by column chromatography (silica gel, eluting with 0-2% acetone in CH_2Cl_2) to give purified **TX63936** (32 mg, 9% yield) as a white solid: m/z = 452.2 (M+1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.05 (s, 1H), 3.30 (d, 1H, J = 4.9 Hz), 2.70 (m, 1H), 2.50 (m, 1H), 1.48 (s, 6H), 1.27 (d, 3H, J = 6.7 Hz), 1.12-2.08 (m, 15H), 1.07 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H).

Compound 75: A mixture of compound **7** (1.16 g, 2.47 mmol), NH_2OH-HCl (398 mg, 5.72 mmol), NaOAc (466 mg, 5.68 mmol), CH_2Cl_2 (12 mL) and MeOH (12 mL) were heated at 60 °C (oil bath temperature) for 1.5 h. EtOAc was added. The mixture was washed with water. Organic extract was dried with $MgSO_4$, and concentrated to give compound **77** (1.20 g) as a white foam solid: m/z 484.3 (M+1). Compound **75** was used in the next step without further purification.

Compound 76: Compound **75** (1.20 g, 2.47 mmol) was dissolved in AcOH (2.9 mL) and Ac_2O (0.35 mL, 3.70 mmol). After the reaction was stirred at room temperature for 1 h, $PhI(OAc)_2$ (1.195 g, 3.71 mmol), $Pd(OAc)_2$ (28 mg, 0.13 mmol, 0.05 eq.) and $ClCH_2CH_2Cl$ (5.8 mL) were added. After the reaction was heated at 60 °C for 15 h, and 80 °C for 3 h, additional amount of $Pd(OAc)_2$ (28 mg, 0.13 mmol, 0.05 eq.) was added. After another 3 h at 80 °C, the reaction was cooled to room temperature. Solvent was removed by evaporation. Aq. $NaHCO_3$ was added. The mixture was extracted with EtOAc. The combined organic extracts were dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give product **76** (629 mg, 44% yield from **7**) as a light orange foam solid. Compound **76** is 3:1 mixture 2 isomers: m/z 584.3 (M+1).

Compound 77: K_2CO_3 (742 mg, 5.37 mmol) was added to a solution of compound **76** (627 mg, 1.07 mmol) in MeOH (22 mL) at 0 °C. After the reaction was stirred at room temperature for 1.5 h, CH_2Cl_2 and 12 N HCl (0.90 mL, 10.8 mmol) were added. After stirring for 5 min, the mixture was transferred to a separatory funnel. Water was added. The product was extracted CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, and concentrated to give compound **77** as a light yellow foam. Compound **77** was a 4.5:1 mixture of 2 isomers: m/z 500.2 (M+1).

Compound 78: A mixture of compound **77** obtained above, $NaHSO_3$ (58.5% SO_2, 410 mg, 3.73 mmol), EtOH (7.5 mL) and water (2.5 mL) were heated at 80 °C for 1 h. Additional amount of $NaHSO_3$ (58.5% SO_2, 100 mg, 0.91 mmol) was added. After the reaction was heated at 80 °C for another 3 h, EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-100% EtOAc in hexanes) to give compound **78** (380 mg, 73% yield from **76**) as a white solid: m/z 485.2 (M+1).

Compound 80: Jones' reagent was added dropwise to a solution of compound **78** (51.6 mg, 0.11 mmol) in acetone (1 mL) at 0 °C until the orange color persisted. The reaction was stirred until compound **78** was completely consumed. EtOAc was added. The mixture was transferred to a separatory funnel, which was washed with water. The organic extract was dried with $MgSO_4$, and concentrated. The crude product, a mixture of compound **79** (m/z = 499.2 (M+1)) and **80** ((m/z = 455.2 (M+1)), was heated at 80 °C for 2 h, and 120 °C for 30 min under vacuum. After cooled to room temperature, the residue was purified by column chromatography (silica gel, eluting with 0-40% EtOAc in hexanes) to give compound **80** (39 mg, 81% yield from **78**) as a white solid: m/z 455.2 (M+1).

Compound 81: NaOMe (279 μL, 1.22 mmol) was added to a mixture of compound **80** (37 mg, 0.08 mmol) and HCO_2Et (196 μL, 2.44 mmol) at 0 °C. After the mixture was stirred at ambient temperature for 10 min, THF (0.3 mL) was added. The reaction was continued at room temperature for 5 h, and cooled to 0 °C. MTBE and 6 N HCl (0.22 mL, 1.32 mmol) were added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The crude product was mixed with NH_2OH-HCl (9 mg, 0.13 mmol), EtOH (4 mL) and water (0.2 mL). After the reaction was heated at 55 °C for 18 h, EtOAc was added. The mixture was transferred

to a separatory funnel, which was washed with water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 10% EtOAc in CH_2Cl_2) to give compound **81** (18 mg, 45% yield) as a white solid: m/z 480.2 (M+1). Compound **81** was contaminated with some impurities.

Compound 82: NaOMe (12 μL, 0.052 mmol) was added to a suspension of compound **81** (17 mg, 0.035 mmol) in MeOH (0.70 mL) and THF (0.35 mL) at room temperature. After the reaction was heated at 55 °C for 2.5 h, additional amount of NaOMe (12 μL, 0.052 mmol) and MeOH (0.70 mL) were added. The mixture was heated at 55 °C for another 1 h, and was cooled to room temperature. MTBE was added. The mixture was transferred to a separatory funnel, which was washed with 1 N aq. HCl, and water. The organic extract was dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0-70% EtOAc in hexanes) to give compound **82** (8.7 mg, 51% yield) as a white solid: m/z 480.2 (M+1).

Compound TX63614: A solution of 1,3-dibromo-5,5-dimethylhydantoin (2.6 mg, 0.009 mmol) in DMF (21 μL) was added to a solution of compound **82** (8.7 mg, 0.018 mmol) in DMF (100 μL) at 0 °C. After the reaction was stirred at 0 °C for 1 hr, pyridine (5 μL, 0.062 mmol) was added. The reaction was heated at 55 °C for 3 h, and was cooled to room temperature. The mixture was diluted with EtOAc, and was transferred to a separatory funnel, which was washed with 1 N aq. HCl, aq. Na_2SO_3 solution, and water. The organic extract was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography (silica gel, eluting with 0% to 50% EtOAc in hexanes) to give **TX63614** (7 mg, 81% yield) as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 6.03 (s, 1H), 3.70 (s, 3H), 3.05 (m, 1H), 2.96 (d, 1H, J = 4.5 Hz), 2.48-2.56 (m, 2H), 2.12 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.15-1.95 (m, 14H), 1.03 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H); m/z 478.2 (M+1).

Compound TX63693: A solution of compound **TX63618** (200 mg, 0.421 mmol) in methanol (20 mL) and benzene (1 ml) was heated at 85 °C for 20 hours. The solvent was removed, and the residue was purified by column chromatography (silica gel, 0 to 80% EtOAc in Hexanes) to give compound **TX63693** (149 mg, 69%) as white foam solid: ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 4.37 (s, 1H), 3.62 (s, 3H), 3.12 (d, 1H, J = 4.6 Hz), 2.71 (m, 1H), 2.49 (m, 1H), 1.46 (s, 3H),

1.45 (s, 3H), 1.26 (d, 3H, J = 6.7 Hz), 1.10-2.10 (m, 15H), 1.04 (s, 3H), 1.02 (s, 3H), 0.90 (s, 3H); m/z 432.2 (M - $NHCO_2CH_3$).

Compound TX63800: A solution of compound **TX63618** (200 mg, 0.421 mmol) in ethanol (20 mL) and benzene (1 ml) was heated at 85 °C for 20 hours. The solvent was removed, and the residue was purified by column chromatography (silica gel, 0 to 75% EtOAc in Hexanes) to give compound **TX63800** (156 mg, 71%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 4.35 (s, 1H), 4.06 (m, 2H), 3.13 (d, 1H, J = 4.5 Hz), 2.70 (m, 1H), 2.48 (m, 1H), 1.45 (s, 6H), 1.26 (d, 3H, J = 6.7 Hz), 1.10-2.06 (m, 18H), 1.03 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H)); m/z 432.2 (M - $NHCO_2CH_2CH_3$).

Compound TX63819: A solution of compound **TX63618** (150 mg, 0.316 mmol) in 2-propanol (20 mL) and benzene (1 ml) was heated at 85 °C for 20 hours. The solvent was removed, and the residue was purified by column chromatography (silica gel, 0 to 60% EtOAc in Hexanes) to give compound **TX63819** (100 mg, 59%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.03 (s, 1H), 4.87 (m, 1H), 4.31 (s, 1H), 3.13 (d, 1H, J = 4.5 Hz), 2.69 (m, 1H), 2.48 (m, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.26 (d, 3H, J = 6.7 Hz), 1.21 (d, 6H, J = 5.6 Hz), 1.10-2.06 (m, 15H), 1.04 (s, 3H), 1.02 (s, 3H), 0.90 (s, 3H); m/z 432.2 (M-$NHCO_2CH(CH_3)_2$).

Compound TX63862: NH_3 in Methanol (2M solution, 0.83ml, 1.67 mmol) was added to a solution of compound **TX63618** (158.6 mg, 0.334 mmol) in THF (2.5ml) at 0°C. The mixture was stirred at room temperature for 4 hours. The solvent was removed, and the residue was purified by trituration in Ethanol to give compound **TX63862** (125 mg, 76%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.02 (s, 1H), 3.15 (d, 1H, J = 4.6 Hz), 1.42 (s, 3H), 1.41 (s, 3H), 1.24 (d, 3H, J = 6.7 Hz), 1.08-2.50 (m, 17 H), 0.99 (s, 3H), 0.98 (s, 3H), 0.87 (s, 3H); m/z 492.2 (M+1)

Compound TX63826: Ethylamine in THF (2M solution, 0.193ml, 0.386 mmol) was added to a solution of compound **TX63618** (152.8 mg, 0.322 mmol) in THF (2.5ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed, and the residue was purified by column chromatography (silica gel, 0 to 90% EtOAc in Hexanes) to give compound **TX63826** (85 mg, 50%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.02 (s, 1H), 4.32 (t, 1H, J = 5.2 Hz), 3.98 (s, 1H), 3.13-3.24 (m, 3H), 2.47 (m, 2H), 2.28 (m, 1H), 2.13 (m, 1H), 1.44

(s, 3H), 1.43 (m, 3H), 1.27 (d, 3H, J = 6.7 Hz), 1.23-1.96 (m, 13H), 1.13 (t, 3H, J = 7.2 Hz), 1.03 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H); m/z 520.3 (M+1).

Compound TX63875: Dimethyl amine in THF (2M solution, 0.195ml, 0.391 mmol) was added to a solution of compound **TX63618** (154.6 mg, 0.325 mmol) in THF (2.5ml). The mixture was stirred at room temperature for 20 hours. The solvent was removed, and the residue was purified by column chromatography (silica gel, 0 to 80% EtOAc in Hexanes) to give compound **TX63875** (108 mg, 63%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.07 (s, 1H), 3.86 (s, 1H), 3.25 (d, 1H, J = 4.5 Hz), 2.91 (s, 6H), 2.59 (m, 1H), 2.51 (m, 1H), 2.30 (m, 1H), 2.15 (m, 1H), 1.48 (s, 6H), 1.29 (d, 3H, J = 6.7 Hz), 1.10-1.97 (m, 13H), 1.06 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H); m/z 520.3 (M+1).

Compound TX63876: Methyl amine in THF (2M solution, 0.187ml, 0.375 mmol) was added to a solution of compound **TX63618** (148.3 mg, 0.312 mmol) in THF (2.5ml). The mixture was stirred at room temperature for 20 hours. The solvent was removed, and the residue was purified by column chromatography (silica gel, 0 to 80% EtOAc in Hexanes) to give compound **TX63876** (100 mg, 63%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.04 (s, 1H), 4.45 (m, 1H), 4.13 (s, 1H), 3.18 (d, 1H, J = 4.6 Hz), 2.79 (d, 3H, J = 4.8 Hz), 2.49 (m, 2H), 2.32 (m, 1H), 2.16 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.29 (d, 3H, J = 6.7 Hz), 1.10-1.97 (m, 13H), 1.05 (s, 6H), 0.92 (s, 3H); m/z 506.3 (M+1).

Compound TX63798: Et_3N (400 μL, 2.88 mmol) and Benzoyl chloride (50 μL, 0.431 mmol) were added sequentially to a solution of compound **TX63620** (129 mg, 0.288 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After the reaction was stirred at 0°C for 1 hr, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 60% EtOAc in hexanes) to give compound **TX63798** (50.4 mg, 31%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.71 (d, 2H, J = 7.6 Hz), 7.49 (t, 1H, J = 7.6 Hz), 7.42 (t, 2H, J = 7.6 Hz), 6.06 (s, 1H), 5.68 (s, 1H), 3.23 (d, 1H, J = 4.5 Hz), 2.77 (m, 1H), 2.46 (m, 2H), 2.19 (m, 1H), 2.01 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.25 (d, 3H, J = 6.6 Hz), 1.19-1.93 (m, 11H), 1.07 (s, 6H), 0.92 (s, 3H);), m/z 553. (M+1).

Compound TX63818: Et_3N (57 μL, 0.408 mmol) and 2,2,2-Trifluoroethyl sulfonyl chloride (39 μL, 0.353 mmol) were added sequentially to a solution of

compound **TX63620** (122 mg, 0.272 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After the reaction was stirred at 0°C for 1 hr, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 60% EtOAc in hexanes) to give compound **TX63818** (77 mg, 47%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.20 (s, 1H), 5.14 (s, 1H), 3.92 (m, 2H), 3.05 (d, 1H, J = 4.4 Hz), 2.64 (m, 1H), 2.48 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.26 (d, 3H, J = 6.7 Hz), 1.12-2.18 (m, 15H), 1.05 (s, 3H), 1.02 (s, 3H), 0.93 (s, 3H); m/z 595.3 (M+1).

Compound TX63863: Cyclobutanecarbonyl chloride (0.152ml, 1.34 mmol) was added at room temperature to a solution of **TX63620** (300 mg, 0.669 mmol), triethylamine (0.466 ml, 3.34 mmol) and DCM (4 ml). The mixture was stirred at room temperature for 2 hours. The organic was washed with 1M HCl, saturated NaHCO3, brine and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 70% EtOAc in hexanes) to give compound **TX63863** (200 mg, 56%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.04 (s, 1H), 4.85 (s, 1H), 3.06 (d, 1H, J = 4.5 Hz), 2.95 (m, 1H), 2.63 (m, 1H), 2.48 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.26 (d, 3H, J = 6.7 Hz), 1.10-2.30 (m, 21H), 1.03 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H); m/z 531.3 (M+1).

Compound TX63864: Propionyl chloride (0.048ml, 0.274 mmol) was added at room temperature to a solution of **TX63620** (123 mg, 0.274 mmol), triethylamine (0.191 ml, 1.37 mmol) and DCM (4 ml). The mixture was stirred at room temperature for 2 hours. The organic was washed with 1M HCl, saturated NaHCO3, brine and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 70% EtOAc in hexanes) to give compound **TX63864** (80 mg, 57%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.04 (s, 1H), 5.01 (s, 1H), 3.07 (d, 1H, J = 4.6 Hz), 2.61 (m, 1H), 2.48 (m, 1H), 2.27 (m, 1H), 2.17 (q, 2H, J = 7.5 Hz), 2.06 (m, 1H), 1.45 (s, 3H), 1.42 (s, 3H), 1.26 (d, 3H, J = 6.7 Hz), 1.14 (t, 3H, J = 7.5 Hz), 1.10-1.95 (m, 13H), 1.03 (s, 6H), 0.89 (s, 3H); m/z 505.3 (M+1).

Compound TX63865: Heptanoyl chloride (0.083ml, 0.539 mmol) was added at room temperature to a solution of **TX63620** (0.121 mg, 0.270 mmol), triethylamine (0.190 ml, 1.36 mmol) and DCM (4 ml). The mixture was stirred at room temperature for 2 hours. The organic was washed with 1M HCl, saturated NaHCO3,

brine and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 70% EtOAc in hexanes) to give compound **TX63865** (110 mg, 72%) as white foam solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.03 (s, 1H), 4.95 (s, 1H), 3.04 (d, 1H, *J* = 4.5 Hz), 2.62 (m, 1H), 2.47 (m, 1H), 2.24 (m, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.10-2.19 (m, 27H), 1.02 (s, 6H), 0.90 (s, 3H), 0.87 (3H, m); m/z 561.4 (M+1).

Compound TX63681: Et_3N (124 μL, 0.89 mmol) and acetic formic anhydride (7.4 M solution prepared in situ, 48 μL, 0.356 mmol) were added sequentially to a solution of compound **TX63620** (80 mg, 0.178 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After the reaction was stirred at 0°C for 1 hr, aq. $NaHCO_3$ was added. The mixture was transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 100% EtOAc in hexanes) to give compound **TX63681** (58 mg, 68%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, 0.45H, *J* = 12.3 Hz), 8.19 (s, 0.55H), 8.03 (s, 0.55H), 8.02 (s, 0.45H), 6.06 (s, 1H), 5.49 (d, 0.45H, *J* = 12.3 Hz), 5.02 (s, 0.55H), 3.14 (d, 0.45H, *J* = 4.5 Hz), 3.09 (d, 0.55H, *J* = 4.5 Hz), 1.48 (s, 3H), 1.46 (s, 3H), 1.27 (d, 3H, *J* = 6.6 Hz), 1.17-2.70 (m, 17H), 1.06 (s, 1.35H), 1.05 (s, 3H), 1.03 (s, 1.65H), 0.94 (s, 1.35H), 0.91 (s, 1.65H); m/z 477.3 (M+ 1).

Compound TX63799: 3,3,3-Trifluoropropionic acid (47 μL, 0.534 mmol) and Et_3N (186 μL, 1.33 mmol) were added sequentially to a solution of compound **TX63620** (200 mg, 0.445 mmol) in CH_2Cl_2 (2 mL) at RT. The solution was cooled at RT, and T3P (50% in EtOAc, 283 mg, 0.891 mmol) was added. After the reaction was stirred at RT for 2 hr, aq. $NaHCO_3$ was added. The mixture was stirred at RT for 1 hr, then transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$ and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography (silica gel, 0 to 50% EtOAc in hexanes) to give compound **TX63799** (50 mg, 20%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.04 (s, 1H), 5.42 (s, 1H), 3.05 (m, 2H), 3.01 (d, 1H, *J* = 4.5 Hz), 2.66 (m, 1H), 2.48 (m, 1H), 2.25 (m, 1H), 2.09 (m, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 1.26 (d, 3H, *J* = 6.7 Hz), 1.16-1.96 (m, 13H), 1.03 (s, 6H), 0.90 (s, 3H); m/z 559.3 (M+1).

Compound TX63866: Cyclopropane carboxylic acid (25 μL, 0.326 mmol) and Et_3N (111 μL, 0.816 mmol) were added sequentially to a solution of compound

TX63620 (122 mg, 0.272 mmol) in CH_2Cl_2 (2 mL) at RT. The solution was cooled at RT, and T3P (50% in EtOAc, 330 μL, 0.543 mmol) was added. After the reaction was stirred at RT for 2 hr, aq. $NaHCO_3$ was added. The mixture was stirred at RT for 1 hr, then transferred to a separatory funnel, which was extracted with EtOAc. The organic extract was washed with aq. $NaHCO_3$ and water, dried with $MgSO_4$, and concentrated. The residue was purified by trituration in EtOH to give compound **TX63866** (60 mg, 42%) as white foam solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.05 (s, 1H), 5.21 (s, 1H), 3.16 (d, 1H, J = 4.5 Hz), 2.64 (m, 1H), 2.49 (m, 1H), 2.25 (m, 1H), 2.02 (m, 1H), 1.46 (s, 6H), 1.26 (d, 3H, J = 6.7 Hz), 1.04 (s, 3H), 1.03 (s, 3H), 0.89 (s, 3H), 0.89-1.96 (m, 16H), 0.69 (m, 2H). m/z 517.3 (M+1).

* * * * * * * * * * * * * * * * *

All of the compounds, compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the disclosure may have only focused on a several 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 compounds, compositions and 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.

The reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the referenced prior art forms part of the common general knowledge in Australia.

REFERENCES

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.

Abraham and Kappas, *Free Radical Biol. Med.,* 39:1-25, 2005.

Ahmad *et al., Cancer Res*., 68:2920-2926, 2008.

Ahmad *et al.*, *J. Biol. Chem.*, 281:35764-9, 2006.

Araujo *et al.*, *J. Immunol.*, 171(3):1572-1580, 2003.

Bach, *Hum. Immunol.,* 67(6):430-432, 2006.

Chauhan and Chauhan, *Pathophysiology*, 13(3):171-181 2006.

Dickerson *et al.*, *Prog Neuropsychopharmacol Biol. Psychiatry,* March 6, 2007.

Dinkova-Kostova *et al., Proc. Natl. Acad. Sci. USA*, 102(12):4584-4589, 2005.

Dudhgaonkar *et al.*, *Eur. J. Pain,* 10(7):573-9, 2006.

Forstermann, *Biol. Chem.*, 387:1521, 2006.

Handbook of Pharmaceutical Salts: Properties, and Use, Stahl and Wermuth Eds.), Verlag Helvetica Chimica Acta, 2002.

Hanson *et al.*, *BMC Medical Genetics*, 6(7), 2005.

Honda *et al. Bioorg. Med. Chem. Lett*., 12:1027–1030, 2002.

Honda *et al.*, *J. Med. Chem*., 43:4233–4246, 2000a.

Honda, *et al.*, *J. Med. Chem.*, 43:1866–1877, 2000b.

Honda *et al.*, *Bioorg. Med. Chem. Lett.*, 7:1623-1628, 1997.

Honda *et al., Bioorg. Med. Chem. Lett.*, 9(24):3429-3434, 1999.

Honda *et al., Bioorg. Med. Chem. Lett.,* 8(19):2711-2714, 1998.

Honda *et al., Bioorg. Med. Chem. Lett.,* 16(24):6306-6309, 2006.

Ishikawa *et al*., *Circulation*, 104(15):1831-1836, 2001.

Kawakami *et al.*, *Brain Dev*., 28(4):243-246, 2006.

Kendall-Tackett, *Trauma Violence Abuse,* 8(2):117-126, 2007.

Kruger *et al.*, *J. Pharmacol. Exp. Ther.*, 319(3):1144-1152, 2006.

Lee *et al.*, *Glia*., 55(7):712-22, 2007.

Lencz *et al.*, *Mol. Psychiatry*, 12(6):572-80, 2007.

Liby *et al., Cancer Res*., 65(11):4789-4798, 2005.

Liby *et al., Nat. Rev. Cancer*, 7(5):357-356, 2007a.

Liby *et al., Mol. Cancer Ther*., 6(7):2113-9, 2007b.

Liby et al., 2007b

Liu *et al.*, *FASEB J.*, 20(2):207-216, 2006.

Lu *et al.*, *J. Clin. Invest.*, 121(10):4015-29, 2011.

March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 2007.

McIver *et al.*, *Pain*, 120(1-2):161-9, 2005.

Morris *et al.*, *J. Mol. Med.*, 80(2):96-104, 2002.

Morse and Choi, *Am. J. Respir. Crit. Care Med.*, 172(6):660-670, 2005.

Morse and Choi, *Am. J. Respir. Crit. Care Med.*, 27(1):8-16, 2002.

Pall, *Med. Hypoth.*, 69:821-825, 2007.

Place *et al., Clin. Cancer Res*., 9(7):2798-806, 2003.

Rajakariar *et al., Proc. Natl. Acad. Sci. USA*, 104(52):20979-84, 2007.

Ross *et al., Am. J. Clin. Pathol.*, 120(Suppl):S53-71, 2003.

Ross *et al., Expert Rev. Mol. Diagn*., 3(5):573-585, 2003.

Ruster *et al.*, *Scand. J. Rheumatol.*, 34(6):460-3, 2005.

Sacerdoti *et al.*, *Curr Neurovasc Res.* 2(2):103-111, 2005.

Salvemini *et al., J. Clin. Invest.*, 93(5):1940-1947, 1994.

Sarchielli *et al.*, *Cephalalgia,* 26(9):1071-1079 , 2006.

Satoh *et al.*, *Proc. Natl. Acad. Sci. USA*, 103(3):768-773, 2006.

Schulz *et al.*, *Antioxid. Redox. Sig.*, 10:115, 2008.

Strejan *et al.*, *J. Neuroimmunol*., 7:27, 1984.

Suh *et al.*, *Cancer Res.*, 58:717–723, 1998.

Suh *et al., Cancer Res*., 59(2):336-341, 1999.

Szabo *et al.*, *Nature Rev. Drug Disc.*, 6:662-680, 2007.

Takahashi *et al.*, *Cancer Res*., 57:1233–1237, 1997.

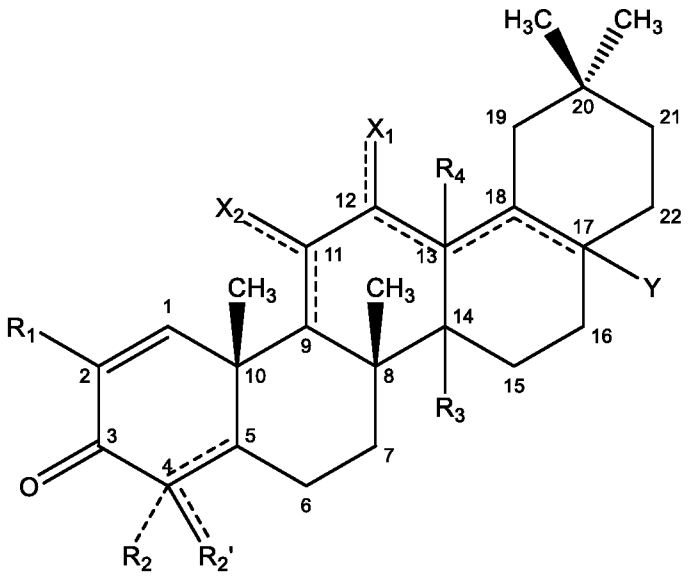
Tamir and Tannebaum, *Biochim. Biophys. Acta*, 1288:F31-F36, 1996.

Xie *et al.*, *J. Biol. Chem*., 270(12):6894-6900, 1995.

Zhou *et al.*, *Am. J. Pathol*., 166(1):27-37, 2005.

CLAIMS

1. A compound of the formula:



(I),

wherein:

X_1 and X_2 are independently hydrogen, halo, hydroxy, amino or oxo, provided that X_1 is not oxo when carbon atoms 12 and 13 are connected to one another with a double bond, further provided that X_2 is not oxo when carbon atoms 9 and 11 are connected to one another with a double bond;

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1\text{-}4)}$, $-NH_2$, $alkylamino_{(C1\text{-}4)}$, or $-NH-S(O)_2-alkyl_{(C1\text{-}4)}$;

R_2 is hydrogen or R_2 is absent when the atom to which it is bound forms part of a double bond;

R_2' is $=CH_2$, $alkyl_{(C\leq 8)}$, or substituted $alkyl_{(C\leq 8)}$;

R_3 and R_4 are each independently hydrogen, hydroxy, methyl or as defined below when either of these groups is taken together with group R_c, provided that R_4 is absent when the atom to which it is bound forms part of a double bond; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

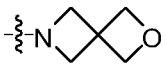
alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 12)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 12)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, alkylthio$_{(C\leq 8)}$, acylthio$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or substituted versions of any of these groups;

−alkanediyl$_{(C\leq 8)}$−R_b, −alkenediyl$_{(C\leq 8)}$−R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, or amino; or

heteroaryl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −OC(O)NH−alkyl$_{(C\leq 8)}$, −OC(O)CH_2NHC(O)O−*t*-butyl, −OCH_2−alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups;

−$(CH_2)_m$C(O)R_c, wherein m is 0–6 and R_c is:

hydrogen, hydroxy, halo, amino, −NHOH, or  ; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −NH−alkoxy$_{(C\leq 8)}$, −NH−heterocycloalkyl$_{(C\leq 8)}$, −NHC(NOH)−alkyl$_{(C\leq 8)}$, −NH−amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_c and R_3, taken together, are −O− or −NR_d−, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

R_c and R_4, taken together, are −O− or −NR_d−, wherein R_d is hydrogen or alkyl$_{(C\leq 4)}$; or

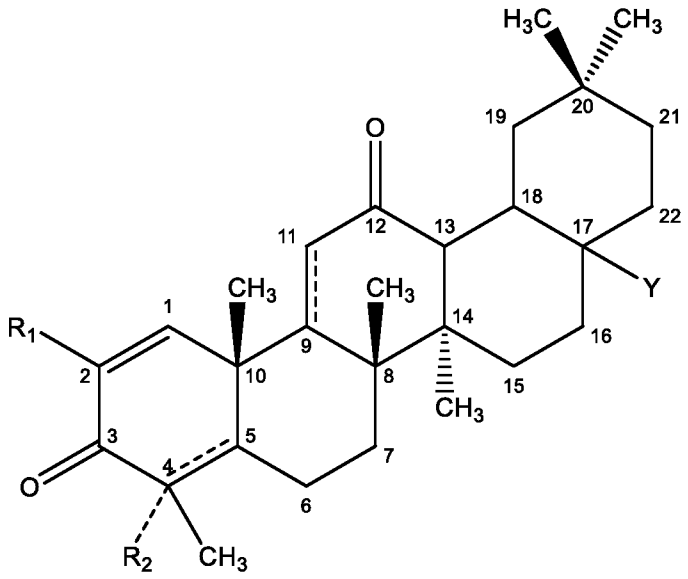
−NHC(O)R_e, wherein R_e is:

hydrogen, hydroxy, amino; or

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(II),

wherein:

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$;

R_2 is hydrogen or R_2 is absent when the atom to which it is bound forms part of a double bond; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq12)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq12)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$,

aralkylamino$_{(C\leq 8)}$, alkylthio$_{(C\leq 8)}$, acylthio$_{(C\leq 8)}$, alkylsulfonyl-amino$_{(C\leq 8)}$, or substituted versions of any of these groups;

−alkanediyl$_{(C\leq 8)}$−R_b, −alkenediyl$_{(C\leq 8)}$−R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, or amino; or

heteroaryl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralk-oxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, alkylsulfonyl-amino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −OC(O)NH−alkyl$_{(C\leq 8)}$, −OC(O)CH_2NHC(O)O−*t*-butyl, −OCH_2−alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups;

−$(CH_2)_m$C(O)R_c, wherein m is 0–6 and R_c is:

hydrogen, hydroxy, halo, amino, −NHOH, or  ; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, hetero-aryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkyl-sulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −NH−alkoxy$_{(C\leq 8)}$, −NH−heterocycloalkyl$_{(C\leq 8)}$, −NHC(NOH)−alkyl$_{(C\leq 8)}$, −NH−amido$_{(C\leq 8)}$, or a substituted version of any of these groups; or

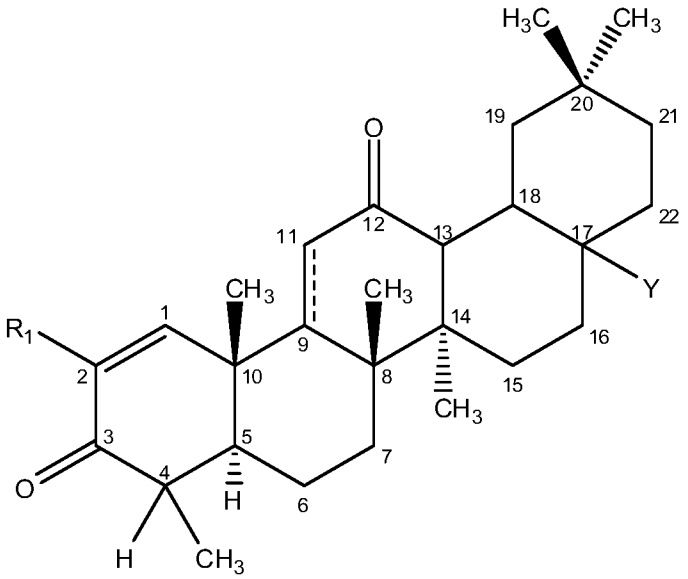
−NHC(O)R_e, wherein R_e is:

hydrogen, hydroxy, amino; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, hetero-aryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkyl-amino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(III),

wherein:

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 12)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $alkylthio_{(C\leq 8)}$, $acylthio_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or substituted versions of any of these groups;

$-alkanediyl_{(C\leq 8)}-R_b$, $-alkenediyl_{(C\leq 8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, or amino; or

$heteroaryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$,

aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, alkylsulfonyl-amino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −OC(O)NH−alkyl$_{(C\leq 8)}$, −OC(O)CH$_2$NHC(O)O−*t*-butyl, −OCH$_2$−alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups;

−(CH$_2$)$_m$C(O)R$_c$, wherein m is 0–6 and R$_c$ is:

hydrogen, hydroxy, halo, amino, −NHOH, or  ; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyl-oxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −NH−alkoxy$_{(C\leq 8)}$, −NH−heterocycloalkyl$_{(C\leq 8)}$, −NHC(NOH)−alkyl$_{(C\leq 8)}$, −NH−amido$_{(C\leq 8)}$, or a substituted version of any of these groups; or

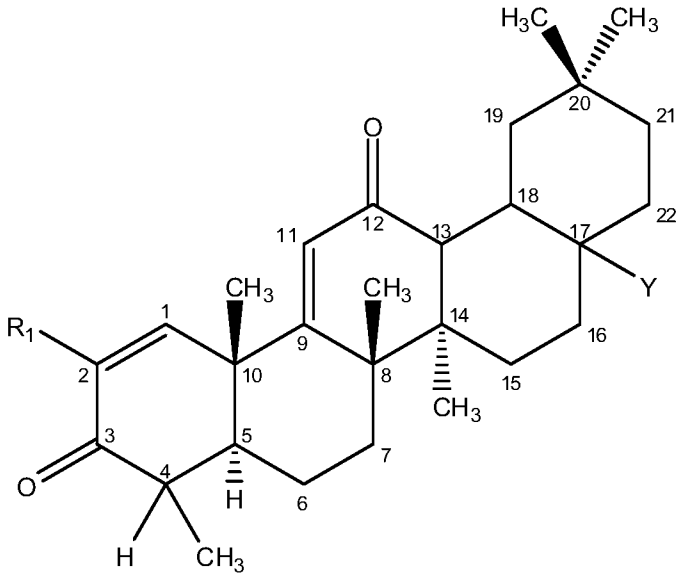
−NHC(O)R$_e$, wherein R$_e$ is:

hydrogen, hydroxy, amino; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(IV),

wherein:

R_1 is −H, −CN, halo, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C1-4)}$, $-NH_2$, $alkylamino_{(C1-4)}$, or $-NH-S(O)_2-alkyl_{(C1-4)}$; and

Y is:

−H, −OH, −SH, −CN, −F, $-CF_3$, $-NH_2$ or −NCO;

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq12)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq12)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkylthio_{(C\leq8)}$, $acylthio_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or substituted versions of any of these groups;

$-alkanediyl_{(C\leq8)}-R_b$, $-alkenediyl_{(C\leq8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, or amino; or

$heteroaryl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $heteroarylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, $-OC(O)NH-alkyl_{(C\leq8)}$,

−OC(O)CH_2NHC(O)O−*t*-butyl, −OCH_2−alkylthio$_{(C\leq 8)}$, or a substituted version of any of these groups;

−$(CH_2)_m$C(O)R_c, wherein m is 0–6 and R_c is:

hydrogen, hydroxy, halo, amino, −NHOH, or  ; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −NH−alkoxy$_{(C\leq 8)}$, −NH−heterocycloalkyl$_{(C\leq 8)}$, −NHC(NOH)−alkyl$_{(C\leq 8)}$, −NH−amido$_{(C\leq 8)}$, or a substituted version of any of these groups; or

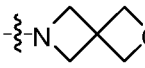
−NHC(O)R_e, wherein R_e is:

hydrogen, hydroxy, amino; or

alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

5. The compound according to any one of claims 1-4, wherein R_1 is −CN.

6. The compound according to any one of claims 1-5, wherein Y is −$(CH_2)_m$C(O)R_c, wherein m is 0–6 and R_c is hydrogen, hydroxy, amino, −NHOH,  , alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, −NH−alkoxy$_{(C\leq 8)}$, −NH−heterocycloalkyl$_{(C\leq 8)}$, −NHC(NOH)−alkyl$_{(C\leq 8)}$, −NH−amido$_{(C\leq 8)}$, or a substituted version of any of these groups other than hydrogen, hydroxy, amino, and –NHOH.

7. The compound of claim 6, wherein R_c is $alkoxy_{(C\leq 8)}$.

8. The compound of claim 6, wherein R_c is hydroxy.

9. The compound of claim 6, wherein R_c is amino.

10. The compound of claim 6, wherein R_c is $alkylamino_{(C\leq 8)}$ or substituted $alkylamino_{(C\leq 8)}$.

11. The compound of claim 6, wherein R_c is $heteroaryl_{(C\leq 8)}$.

12. The compound of claim 6, wherein R_c is $heterocycloalkyl_{(C\leq 8)}$ or substituted $heterocycloalkyl_{(C\leq 8)}$.

13. The compound according to any one of claims 1-12, wherein m is 0.

14. The compound according to any one of claims 1-12, wherein m is 2.

15. The compound according to any one of claims 1-5, wherein Y is $-alkanediyl_{(C\leq 8)}-R_b$.

16. The compound of claim 15, wherein R_b is $acyloxy_{(C\leq 8)}$ or substituted $acyloxy_{(C\leq 8)}$.

17. The compound according to any one of claims 1-5, wherein Y is $heteroaryl_{(C\leq 8)}$.

18. The compound according to any one of claims 1-5, wherein Y is $-NHC(O)R_e$, wherein R_e is hydrogen, hydroxy, amino, $alkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, or substituted version of any of these groups other than hydrogen, hydroxy and amino.

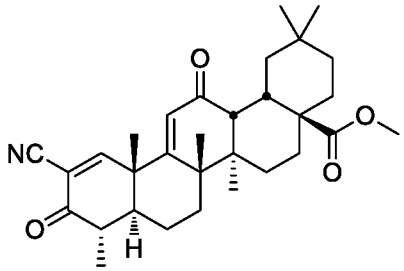
19. The compound of claim 18, wherein R_e is $alkyl_{(C\leq 8)}$ or substituted $alkyl_{(C\leq 8)}$.

20. The compound of claim 18, wherein R_e is $aryl_{(C\leq 8)}$.

21. The compound of claim 18, wherein R_e is $alkoxy_{(C\leq 8)}$.

22. The compound of claim 18, wherein R_e is $alkylamino_{(C\leq 8)}$ or $dialkylamino_{(C\leq 8)}$.

23. The compound of claim 1, further defined as: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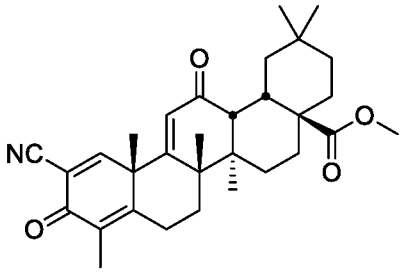
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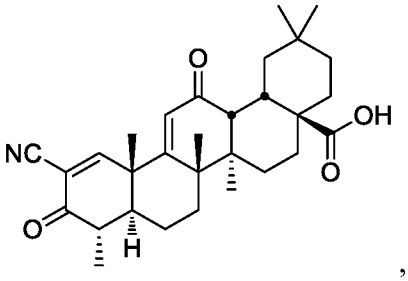
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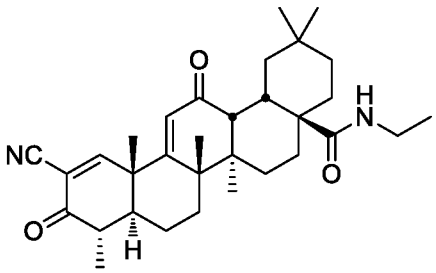
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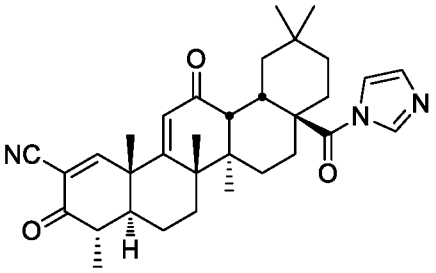
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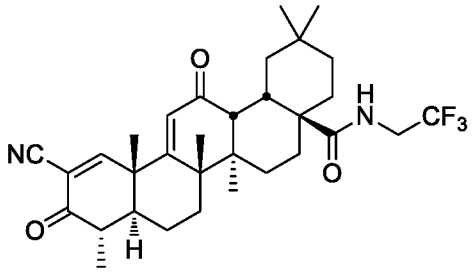
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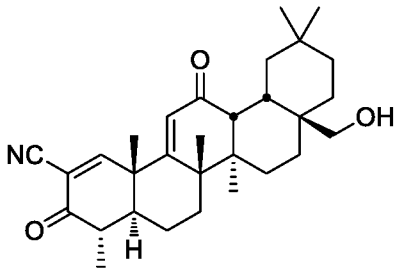
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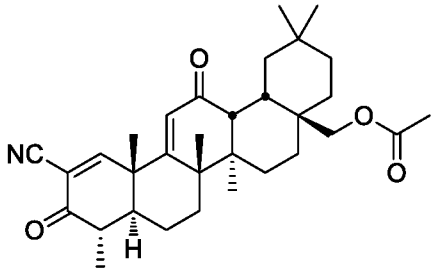
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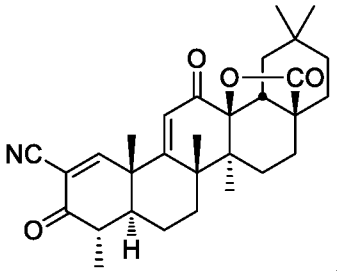
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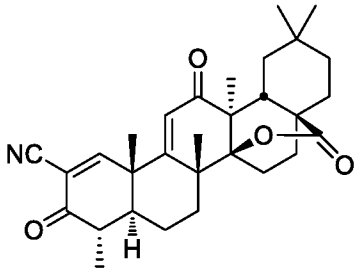
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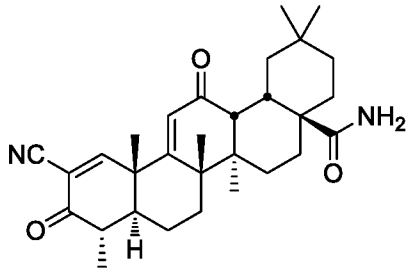
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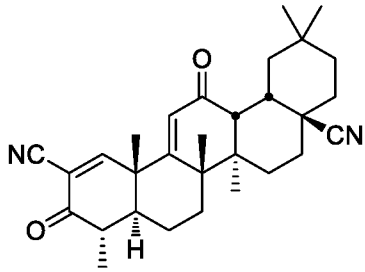
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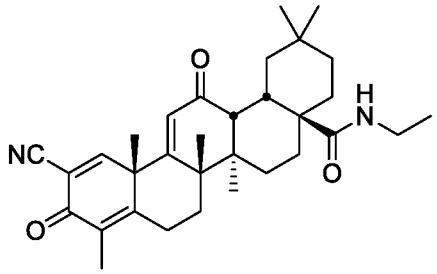

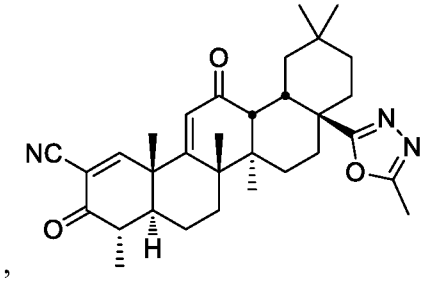
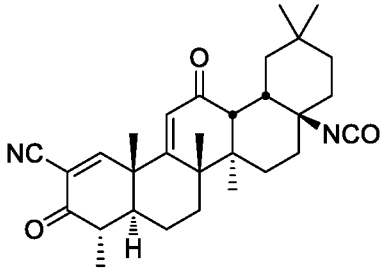
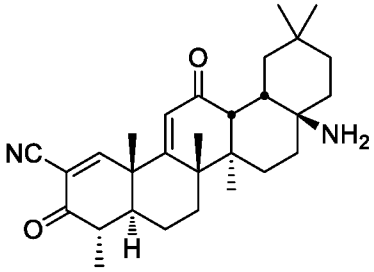
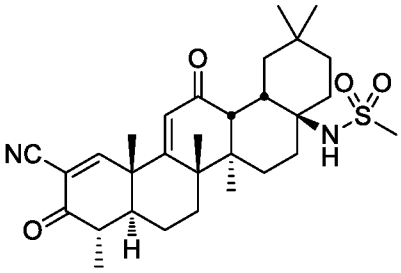
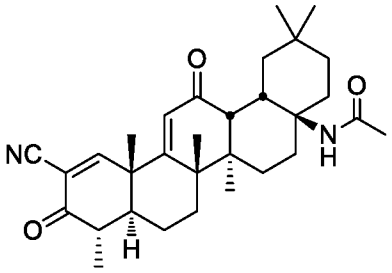
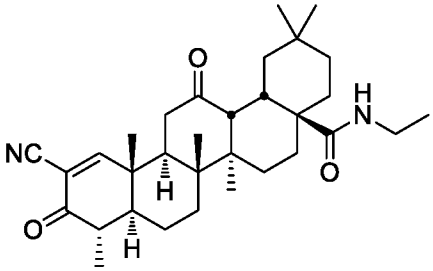
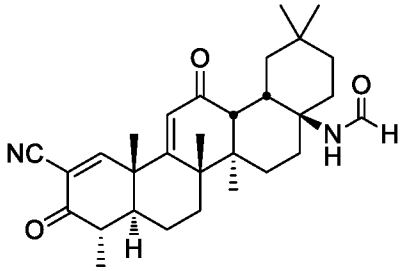
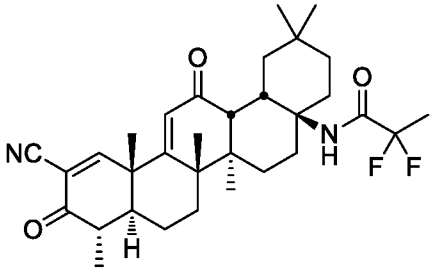
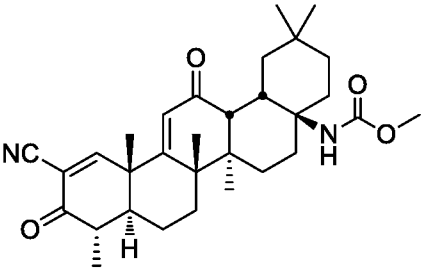
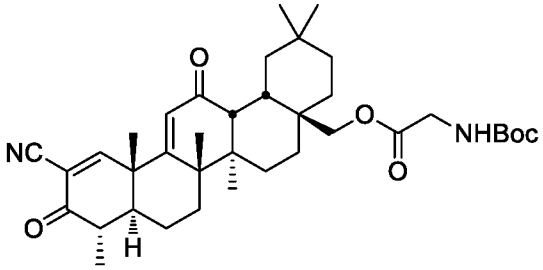
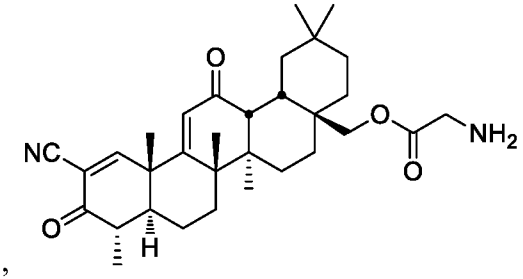
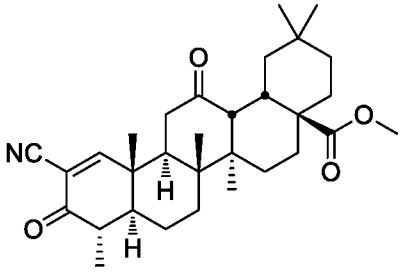
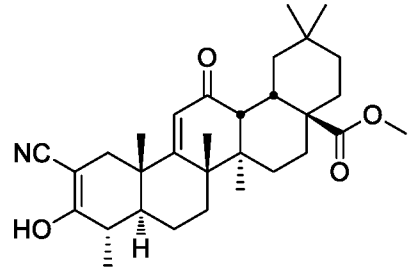
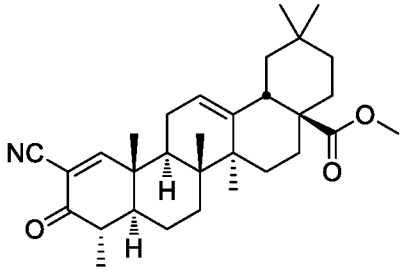

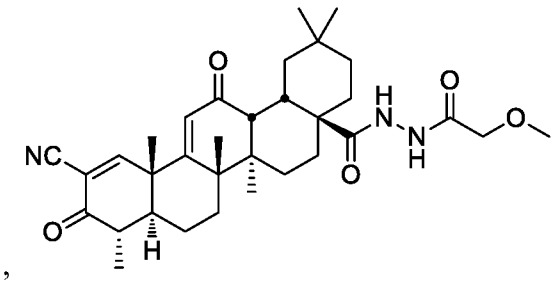
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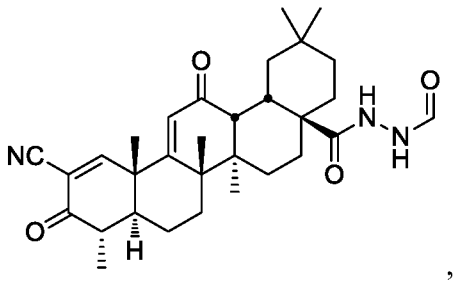
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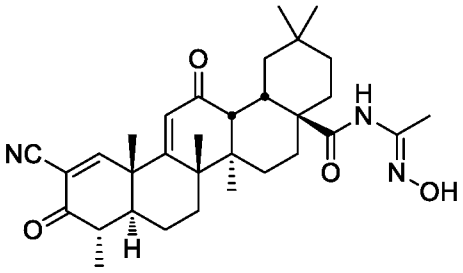
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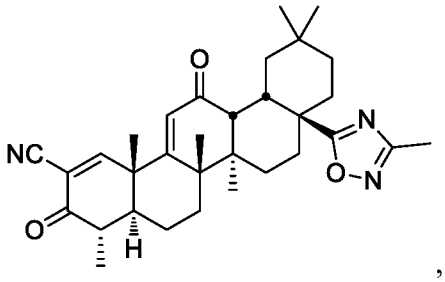
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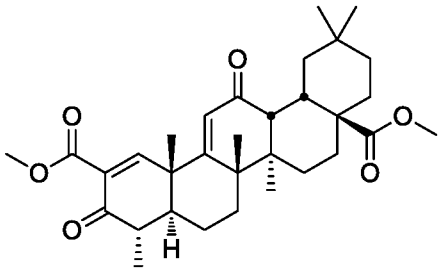
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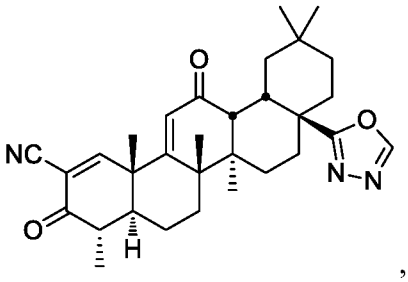
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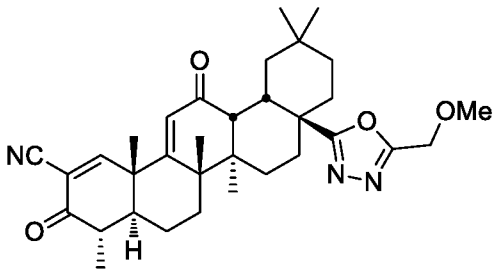
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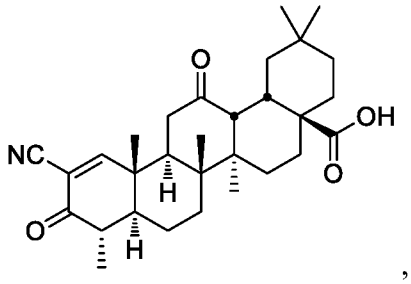
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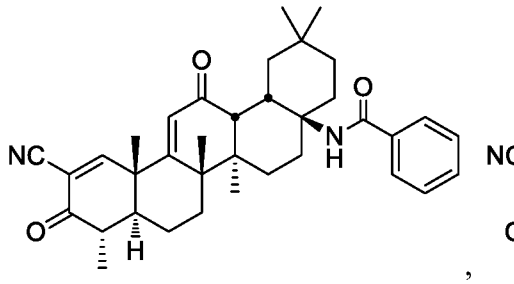
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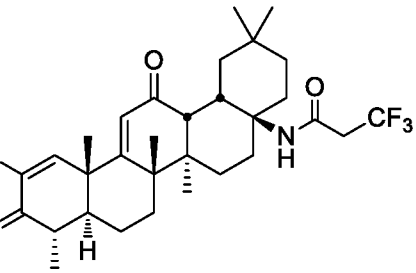
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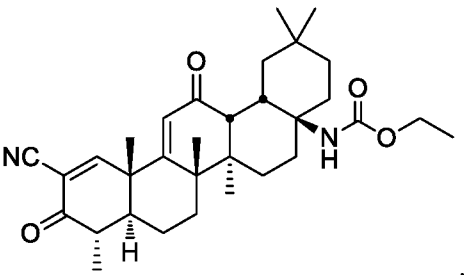
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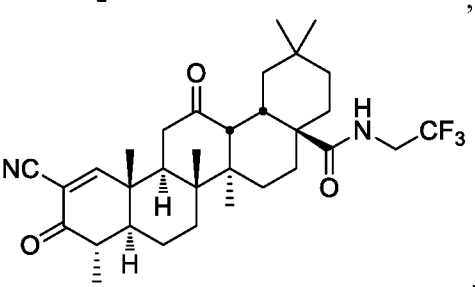
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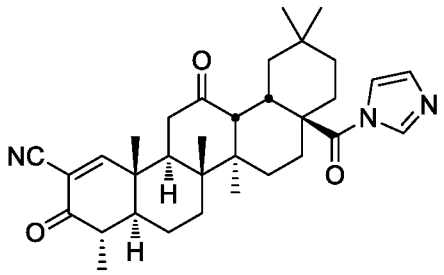
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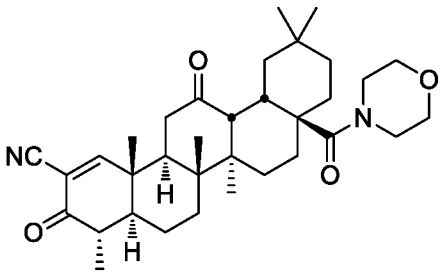
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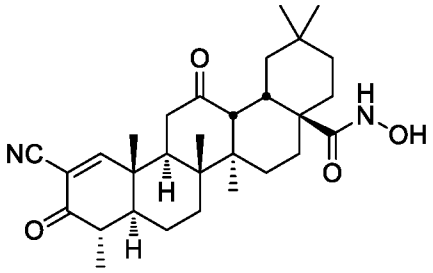
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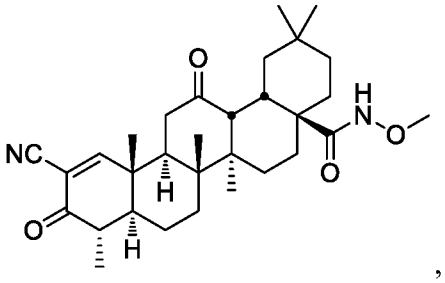
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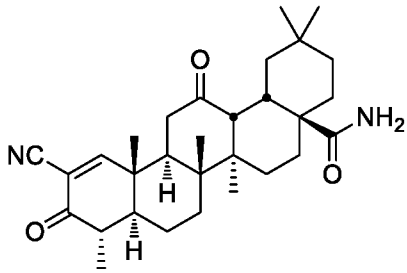
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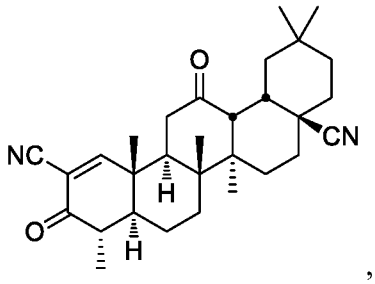
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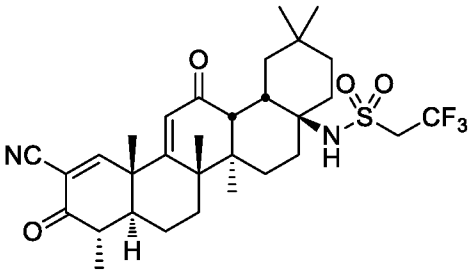
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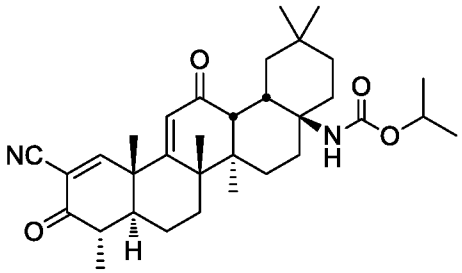
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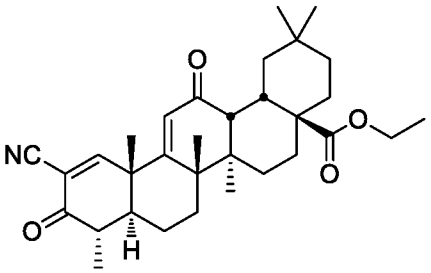
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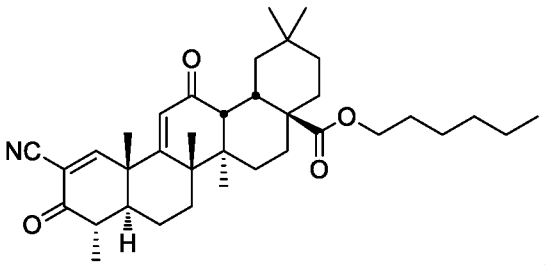
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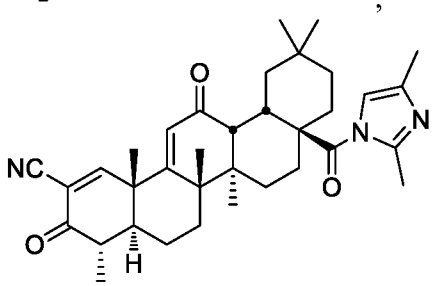
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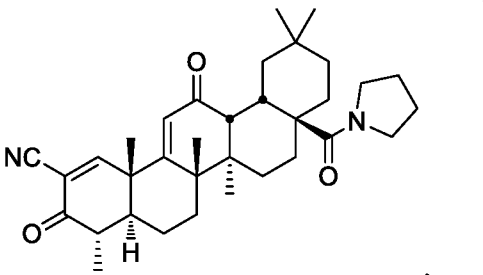
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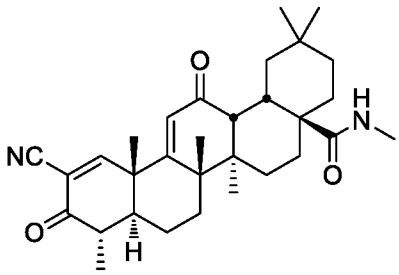
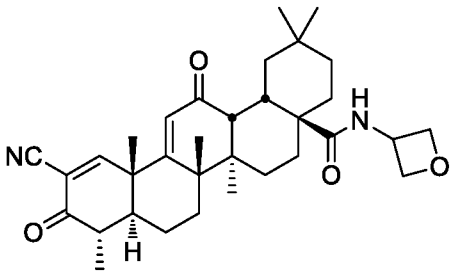
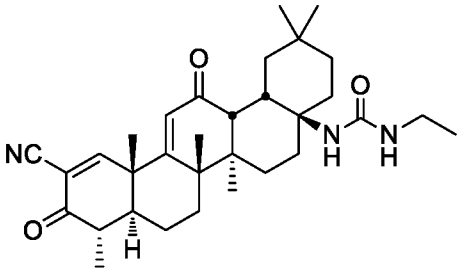
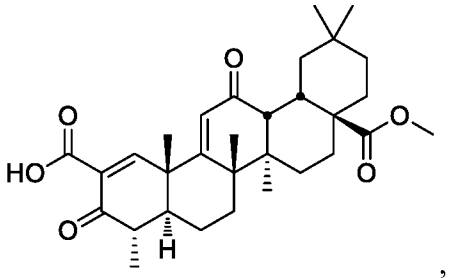
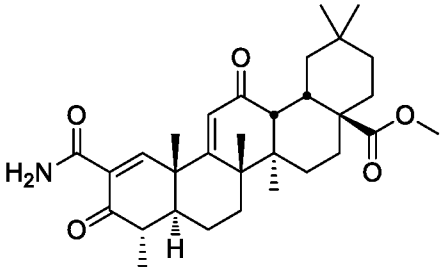
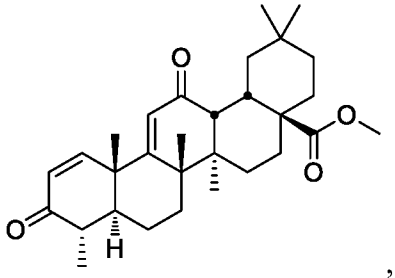
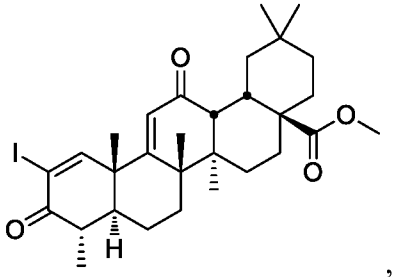
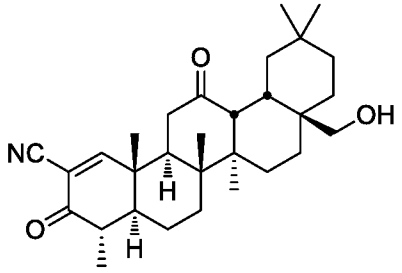
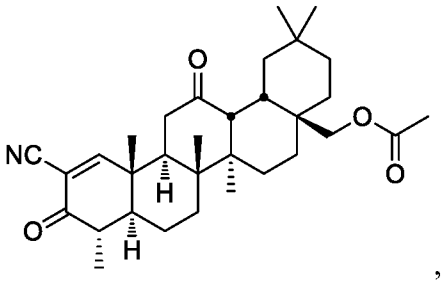

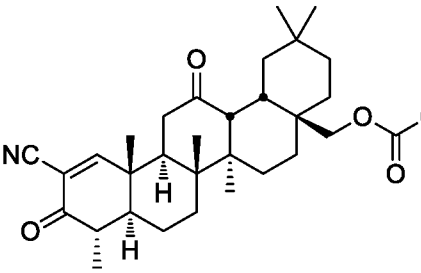
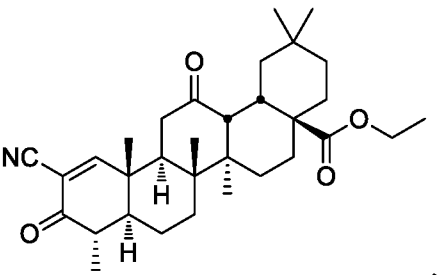
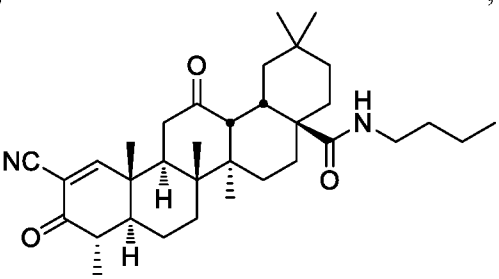

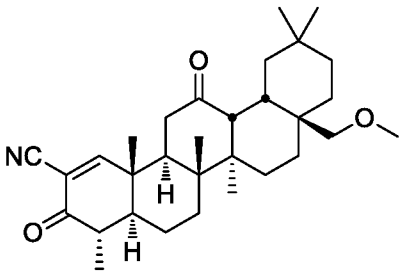
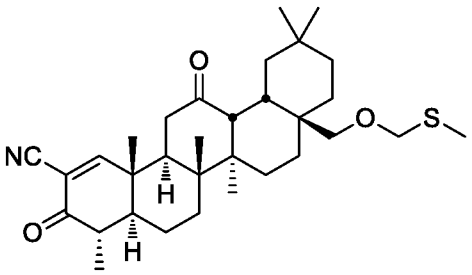
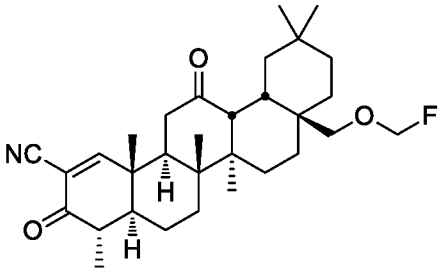
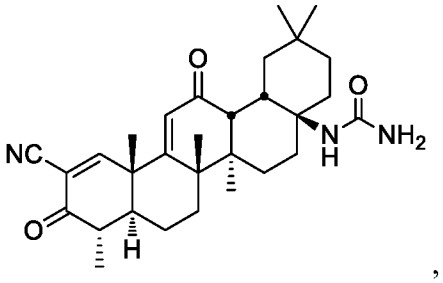
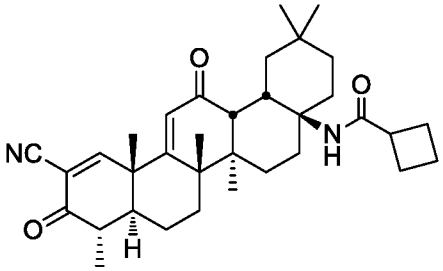
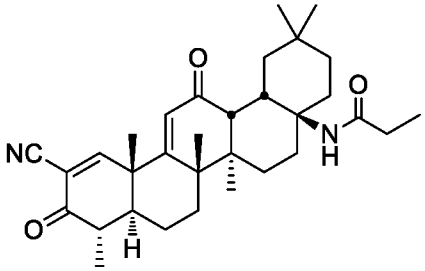
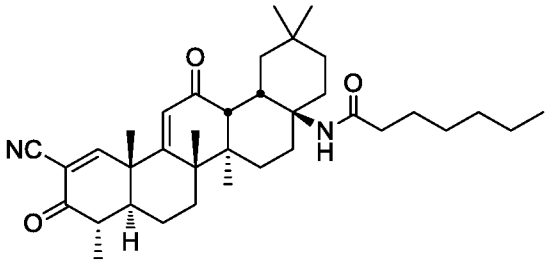
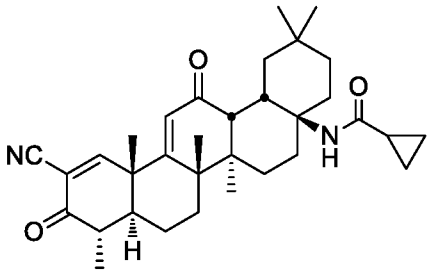
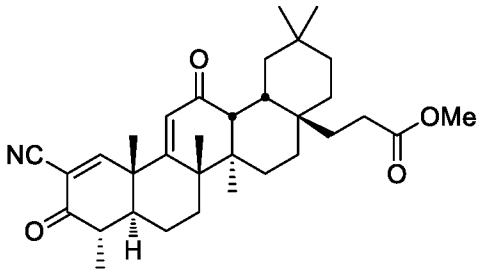
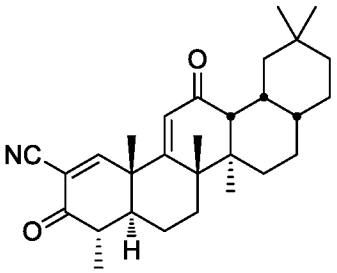
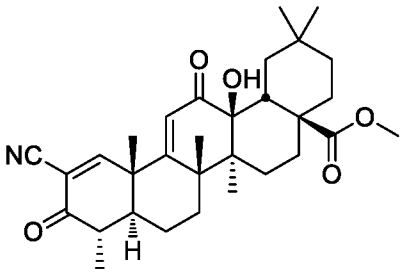
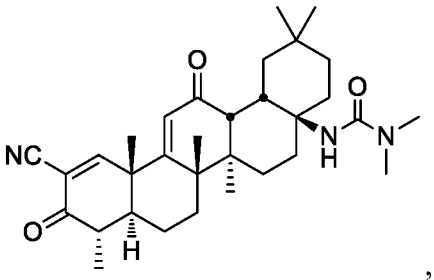

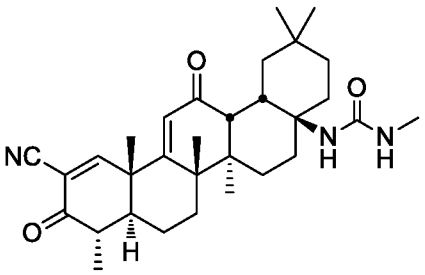
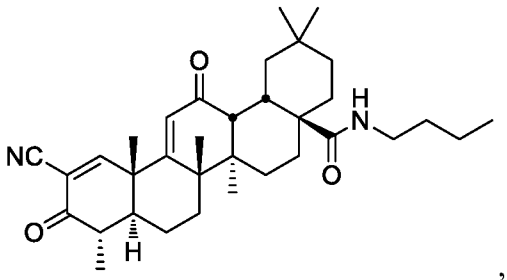
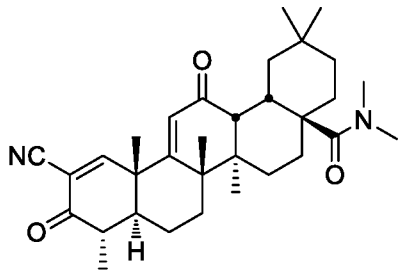
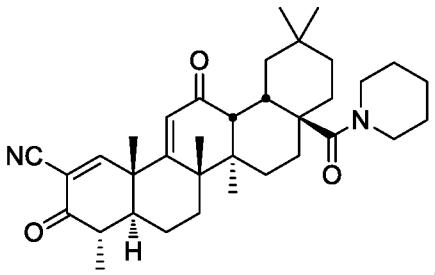
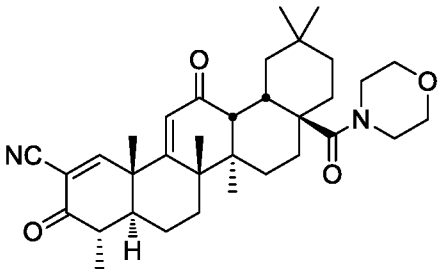
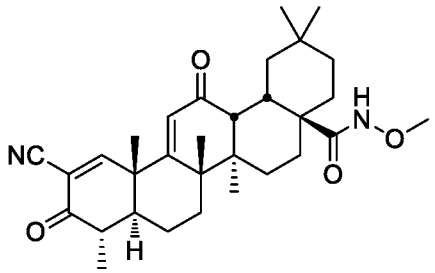
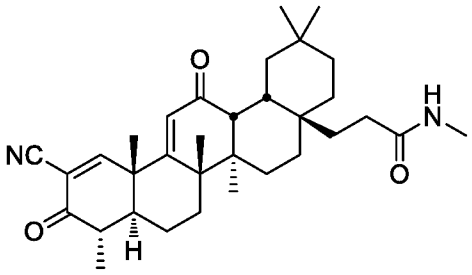
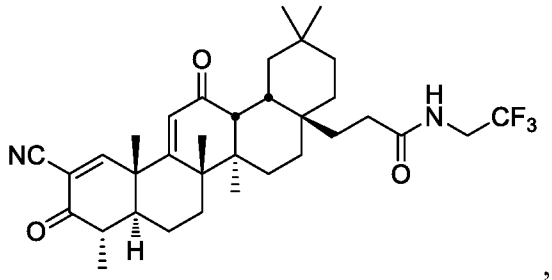
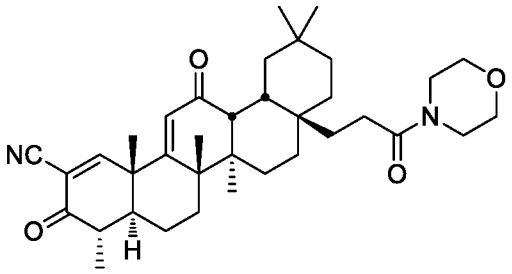
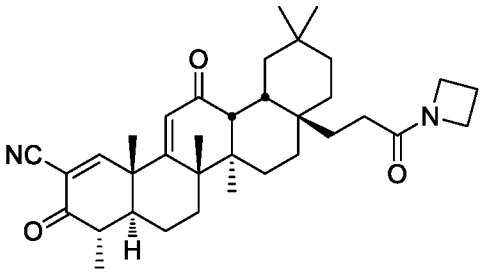
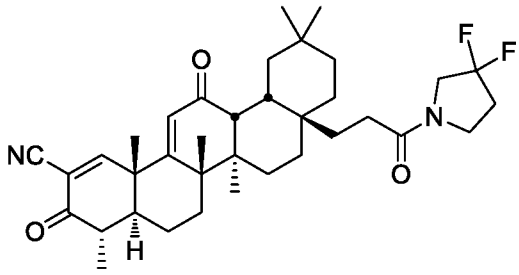
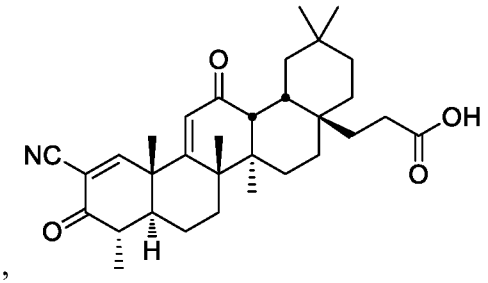


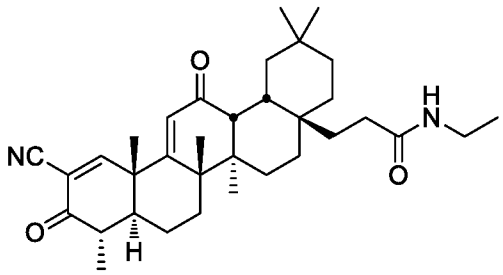
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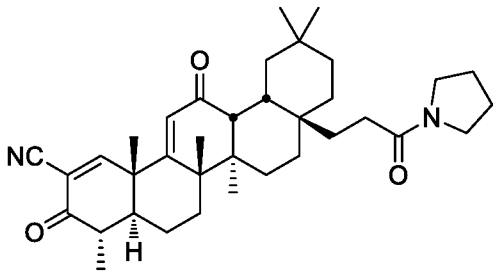
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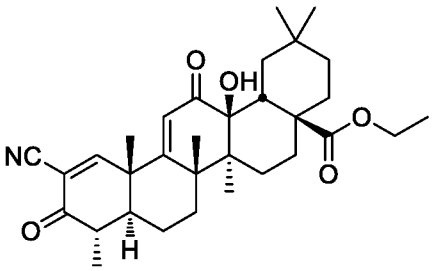
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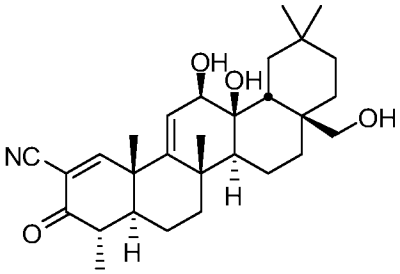
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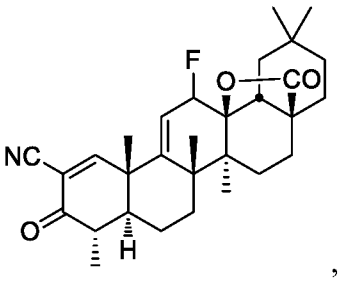
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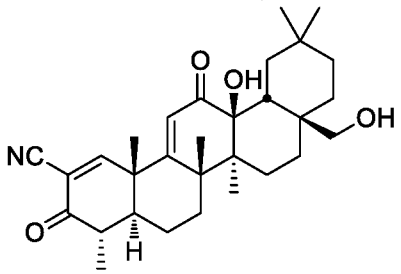
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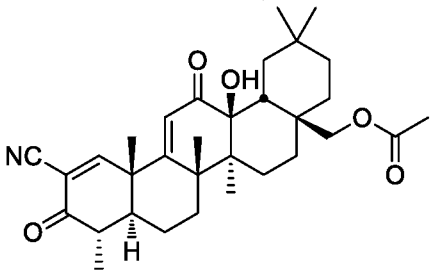
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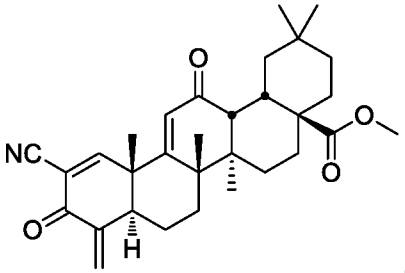
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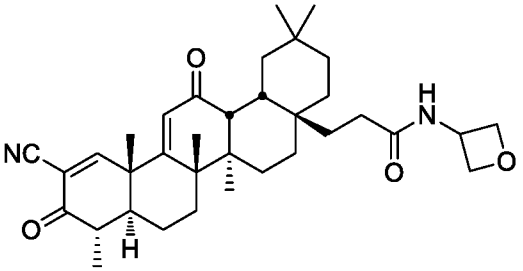
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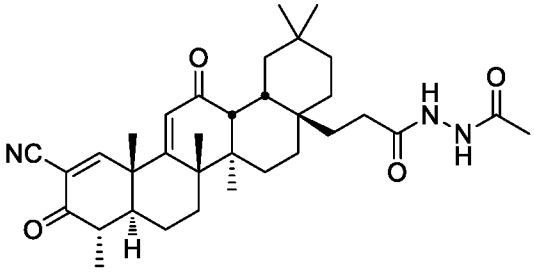
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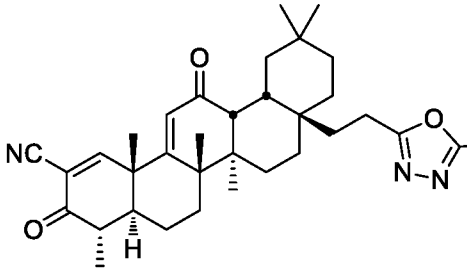
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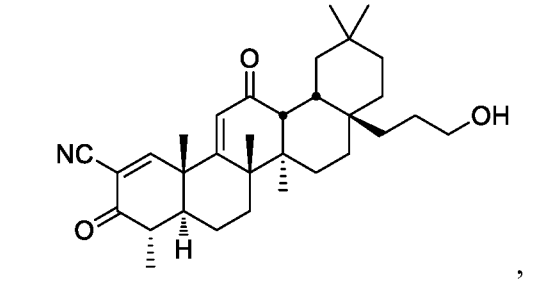
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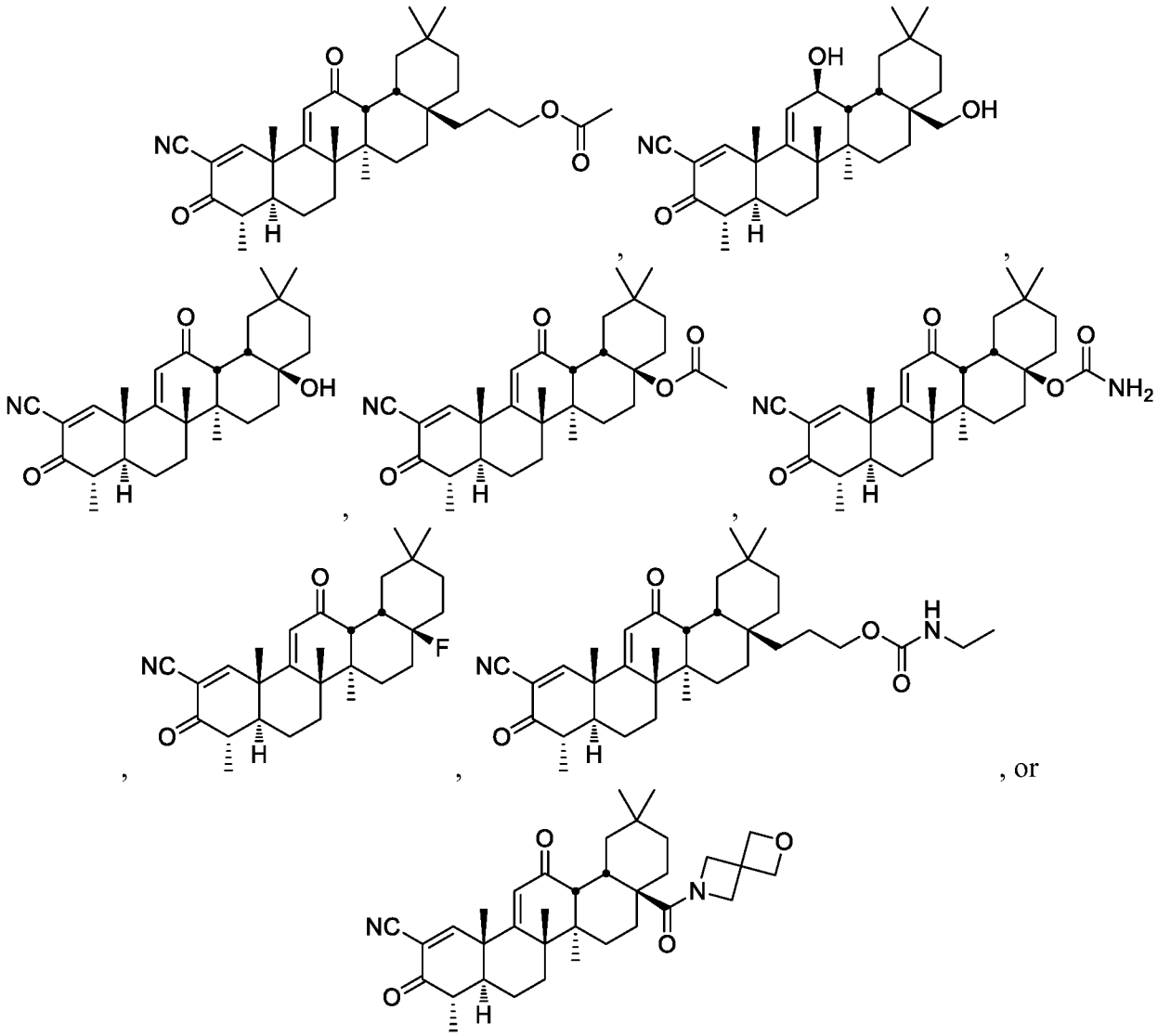

or a pharmaceutically acceptable salt or tautomer thereof.

24. A pharmaceutical composition comprising:

a) the compound according to any one of claims 1-23; and

b) an excipient.

25. A method of treating and/or preventing a disease or a disorder in a patient in need thereof, comprising administering to the patient a compound according to any one of claims 1-23 in an amount sufficient to treat and/or prevent the disease or disorder, wherein the method comprises the suppression of NO production in the patient.

SEQUENCE LISTING

<110> ANDERSON, ERIC
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<120> C4-MONOMETHYL TRITERPENOID DERIVATIVES AND METHODS OF USE THEREOF

<130> REAT.P0068WO

<140> UNKNOWN
<141> 2012-03-09

<150> 61/452,017
<151> 2011-03-11

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<223> Synthetic primer

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