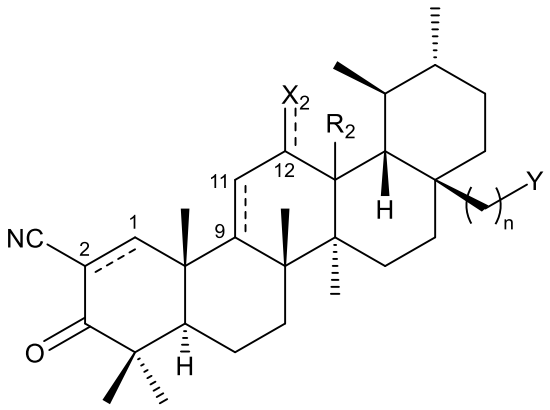
SUMMARY

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-A),

wherein:

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

the bond between atom 9 and atom 11 is a single bond or a double bond;

the bond between atom 12 and X_2 is a single bond or a double bond;

n is 0–6;

X_2 is oxo, or X_2 is taken together with Y as defined below, provided that when X_2 is oxo, then the bond between atom 12 and X_2 is a double bond, and when X_2 is taken together with Y as defined below, that the bond between atom 12 and X_2 is a single bond;

R_2 is hydrogen or hydroxy; or R_2 is taken together with Y as defined below; and

Y is hydrogen, hydroxy, halo, or amino; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, or a substituted version of any of these groups; or

$-arenediyl_{(C\leq12)}-R_3$, substituted $-arenediyl_{(C\leq12)}-R_3$, $-heteroarenediyl_{(C\leq12)}-R_3$, or substituted $-heteroarenediyl_{(C\leq12)}-R_3$, wherein:

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

Y is taken together with R_2 and is $-(CH_2)_mX_1-$, wherein:

m is 0–6; and

X_1 is −O−; or

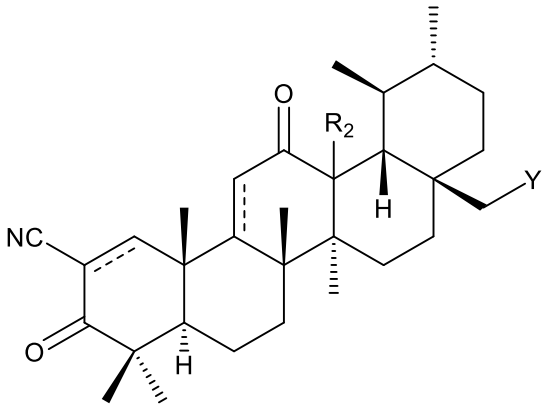
Y is taken together with X_2 and is $-(CH_2)_oC(O)-$, wherein:

o is 0-6; and

X_2 is −O−;

or a pharmaceutically acceptable salt thereof.

In some examples, the compound is further defined as:



(I),

wherein:

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

the bond between atom 9 and atom 11 is a single bond or a double bond;

n is 0–6;

R_2 is hydrogen or hydroxy; or R_2 is taken together with Y as defined below; and

Y is hydrogen, hydroxy, halo, or amino; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, or a substituted version of any of these groups; or

$-arenediyl_{(C\leq12)}-R_3$, substituted $-arenediyl_{(C\leq12)}-R_3$, $-heteroarenediyl_{(C\leq12)}-R_3$, or substituted $-heteroarenediyl_{(C\leq12)}-R_3$, wherein:

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

$-alkanediyl_{(C\leq12)}-R_4$ or substituted $-alkanediyl_{(C\leq12)}-R_4$, wherein:

R_4 is $alkoxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of any of these groups; or

−alkanediyl$_{(C\leq12)}$C(O)−R_5 or substituted −alkanediyl$_{(C\leq12)}$−C(O)R_5, wherein:

R_5 is hydroxy or amino; or

alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−C(O)R_7, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, substituted heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, substituted cycloalkylamino$_{(C\leq12)}$, -NHC(NH)-alkyl$_{(C\leq12)}$, or -NHOR_{13}, wherein:

R_{13} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; or

−NR_8R_9, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$, or

−CO_2R_{10}, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−C(O)R_{12}, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−CH=NOR_{11}, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; or

Y is taken together with R_2 and is −$(CH_2)_mX_1$−, wherein:

m is 0–6; and

X_1 is −O−;

or a pharmaceutically acceptable salt thereof.

In further examples, the compound is further defined as:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$, or

$-CO_2R_{10}$, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-C(O)R_{12}$, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-CH=NOR_{11}$, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; or

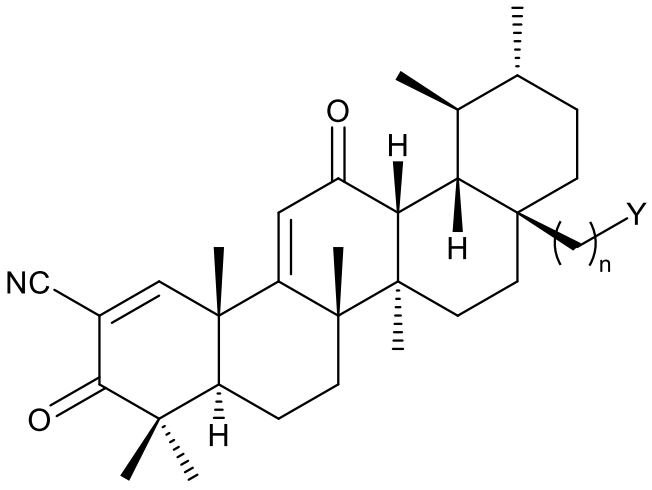
Y is taken together with R_2 and is $-(CH_2)_mX_1-$, wherein:

m is 0–6;

X_1 is $-O-$;

or a pharmaceutically acceptable salt thereof.

In still further examples, the compound is further defined as:



(III),

wherein:

n is 0–6;

Y is hydrogen, hydroxy, halo, or amino; or

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−CH=NOR$_{11}$, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof. In some examples, the bond between atom 1 and atom 2 is a double bond or an epoxidized double bond. In some examples, the bond between atom 1 and atom 2 is a double bond. In other examples, the bond between atom 1 and atom 2 is an epoxidized double bond. In some examples, the bond between atom 9 and atom 11 is a single bond. In other examples, the bond between atom 9 and atom 11 is a double bond. In some examples, X_2 is oxo. In some examples, n is 0, 1, or 2. In some examples, n is 0. In other examples, n is 1. In still other examples, n is 2.

In some examples, Y is hydrogen, hydroxy, halo, or amino; or

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−arenediyl$_{(C\leq12)}$−R_3, substituted −arenediyl$_{(C\leq12)}$−R_3, −heteroarenediyl$_{(C\leq12)}$−R_3, or substituted −heteroarenediyl$_{(C\leq12)}$−R_3, wherein:

R_3 is alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−alkanediyl$_{(C\leq12)}$−R_4 or substituted −alkanediyl$_{(C\leq12)}$−R_4, wherein:

R_4 is alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, or a substituted version of any of these groups; or

−alkanediyl$_{(C\leq12)}$C(O)−R_5 or substituted −alkanediyl$_{(C\leq12)}$−R_5, wherein:

R_5 is hydroxy or amino; or

alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups.

In some examples, Y is amino; or

alkyl$_{(C\leq12)}$, amido$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−heteroarenediyl$_{(C\leq12)}$−R_3 or substituted −heteroarenediyl$_{(C\leq12)}$−R_3, wherein:

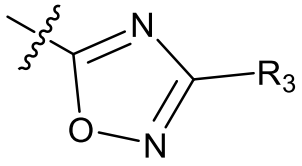
R_3 is alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups); or

−alkanediyl$_{(C\leq12)}$−R_4 or substituted −alkanediyl$_{(C\leq12)}$−R_4, wherein:

R_4 is alkoxy$_{(C\leq12)}$ or substituted alkoxy$_{(C\leq12)}$.

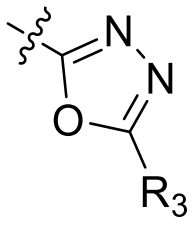
In some examples, Y is amino. In other examples, Y is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In further examples, Y is substituted alkyl$_{(C\leq12)}$, such as hydroxymethyl or methylaminomethyl. In still other examples, Y is amido$_{(C\leq12)}$ or substituted amido$_{(C\leq12)}$. In further examples, Y is amido$_{(C\leq12)}$, such as acetamido or propionamido. In other examples, Y is substituted amido$_{(C\leq12)}$, such as 2,2-difluoropropionamido or 2,2-difluoroacetamido. In yet other examples, Y is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12)}$. In some examples, Y is heterocycloalkyl$_{(C\leq12)}$, such as oxazolidin-3-ylmethyl or azetidin-1-yl. In other examples, Y is substituted heterocycloalkyl$_{(C\leq12)}$, such as 2-oxooxazolidin-3-yl, 3-methyl-2-oxoimidazolidin-1-yl, 2-oxoimidazolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, methyl 3-oxopyrazolidine-1-carboxylate, 5-oxopyrazolidin-1-yl, 2-oxoazetidin-1-yl and 2-oxopyrrolidin-1-yl. In other examples, Y is heteroaryl$_{(C\leq12)}$ or substituted heteroaryl$_{(C\leq12)}$. In further examples, Y is heteroaryl$_{(C\leq12)}$, such as 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 1H-pyrazol-1-yl, 1H-1,2,4-triazol-1-yl, 4-methyl-1H-1,2,3-triazol-1-yl, 1H-tetrazol-1-yl, 1H-1,2,3-triazol-1-yl, 1H-imidazol-1-yl, 5-methyl-1,3,4-oxadiazol-2-yl, or 5-methyl-1,2,4-oxadiazol-3-yl. In other examples, Y is substituted heteroaryl$_{(C\leq12)}$, such as 4-bromo-1H-pyrazol-1-yl, 3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl, 3-(methoxymethyl)-1,2,4-oxadiazol-5-yl, 3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl, 3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl, 3-((dimethylamino)methyl)-1,2,4-oxadiazol-5-yl, 3-(1-methoxyethyl)-1,2,4-oxadiazol-5-yl, or 3-(fluoromethyl)-1,2,4-oxadiazol-5-yl..

In still other examples, Y is −heteroarenediyl$_{(C\leq12)}$−R_3 or substituted −heteroarenediyl$_{(C\leq12)}$−R_3. In further examples, Y is −heteroarenediyl$_{(C\leq12)}$−R_3. In still further examples, Y is a group of the formula:



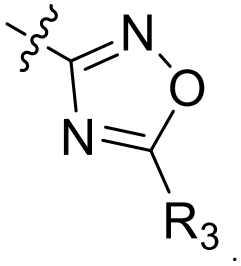
.

In other examples, Y is a group of the formula:



.

In still other examples, Y is a group of the formula:



In some examples, R_3 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$. In further examples, R_3 is $alkyl_{(C\leq12)}$, such as methyl or ethyl. In other examples, R_3 is substituted $alkyl_{(C\leq12)}$, such as 2-methoxyethyl, methoxymethyl, 2-hydroxyethyl, hydroxymethyl, (dimethylamino)methyl, 1-methoxyethyl, or fluoromethyl. In some examples, R_3 is polar-substituted $alkyl_{(C\leq12)}$. In further examples, R_3 is monopolar-substituted $alkyl_{(C\leq12)}$. In still further examples, $monoaminoalkyl_{(C\leq12)}$, $monofluoroalkyl_{(C\leq12)}$, or $monohydroxyalkyl_{(C\leq12)}$. In further examples, R_3 is $monofluoroalkyl_{(C\leq12)}$ or $monohydroxyalkyl_{(C\leq12)}$. In still further examples, R_3 is $monohydroxyalkyl_{(C\leq12)}$, such as 2-hydroxyethyl or hydroxymethyl. In other examples, R_3 is $monofluoroalkyl_{(C\leq12)}$, such as fluoromethyl. In other examples, R_3 is $cycloalkyl_{(C\leq12)}$ or substituted $cycloalkyl_{(C\leq12)}$. In further examples, R_3 is $cycloalkyl_{(C\leq12)}$, such as cyclopropyl. In still other examples, R_3 is $-alkanediyl_{(C\leq12)}-R_4$ or substituted $-alkanediyl_{(C\leq12)}-R_4$. In further examples, R_3 is $-methanediyl-R_4$. In some examples, R_4 is $alkoxy_{(C\leq12)}$, such as *t*-butoxy.

In some examples, Y is $-alkanediyl_{(C\leq12)}-C(O)R_5$ or substituted $-alkanediyl_{(C\leq12)}-C(O)R_5$, wherein:

R_5 is hydroxy or amino; or

$alkoxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $cycloalkylamino_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, or a substituted version of any of these groups.

In some examples, R_5 is hydroxy. In other examples, R_5 is amino. In still other examples, R_5 is $alkoxy_{(C\leq12)}$, such as methoxy. In some examples, R_5 is $alkylamino_{(C\leq12)}$, such as methylamino or ethylamino. In other examples, R_5 is substituted $alkylamino_{(C\leq12)}$, such as 2,2-difluoroethan-1-amino. In some examples, R_5 is $cycloalkyl_{(C\leq12)}$ or substituted $cycloalkyl_{(C\leq12)}$. In further examples, R_5 is $cycloalkyl_{(C\leq12)}$, such as cyclopropyl. In some examples, R_5 is $cycloalkylamino_{(C\leq12)}$ or substituted $cycloalkylamino_{(C\leq12)}$. In further examples,

R_5 is cycloalkylamino$_{(C\leq12)}$, such as cyclopropylamino. In some examples, R_5 is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12).}$ In further examples, R_5 is heterocycloalkyl$_{(C\leq12)}$, such as azetidine or pyrrolidine.

In some examples, Y is

$-C(O)R_7$, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$, -NHC(NH)-alkyl$_{(C\leq12)}$, or -NHOR$_{13(C\leq12)}$, wherein:

R_{13} is hydrogen, alkyl, or substituted alkyl; or

$-NR_8R_9$, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$, or

$-CO_2R_{10}$, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-C(O)R_{12}$, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$ or a substituted version of any of these groups; or

$-CH=NOR_{11}$, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$.

In further examples, Y is $-C(O)R_7$, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$, -NHC(NH)-alkyl$_{(C\leq12)}$, or -NHOR$_{13(C\leq12)}$, wherein:

R_{13} is hydrogen, alkyl, or substituted alkyl.

In some examples, R_7 is hydrogen. In other examples, R_7 is cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$. In further examples, R_7 is cycloalkylamino$_{(C\leq12),}$ such as cyclopropylamino. In some examples, R_7 is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12)}$. In further examples, R_7 is heterocycloalkyl$_{(C\leq12),}$ such as azetidine or

pyrrolidine. In some examples, R_7 is -NHC(NH)-alkyl$_{(C\leq12)}$, such as -NHC(NH)CH_3. In some examples, R_7 is -NHO$R_{13(C\leq12)}$, wherein:

R_{13} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$.

In some examples, R_{13} is hydrogen. In other examples, R_{13} is alkyl$_{(C\leq12)}$, such as methyl.

In some examples, Y is$-NR_8R_9$, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$; or

$-CO_2R_{10}$, wherein

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-C(O)R_{12}$, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups.

In some examples, R_8 is hydrogen. In other examples, R_8 is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In further examples, R_8 is alkyl$_{(C\leq12)}$, such as methyl. In some examples, R_9 is acyl$_{(C\leq12)}$ or substituted acyl$_{(C\leq12)}$. In further examples, R_9 is acyl$_{(C\leq12)}$, such as acetyl, methylacetyl, cyclopropylcarboxyl, or cyclobutylcarboxyl. In other examples, R_9 is substituted acyl$_{(C\leq12)}$, such as methylaminocarbonyl, difluoroacetyl, or difluoromethylacetyl. In some examples, R_9 is alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, or substituted cycloalkylsulfonyl$_{(C\leq12)}$. In further examples, R_9 is alkylsulfonyl$_{(C\leq12)}$, such as is methylsulfonyl or ethylsulfonyl. In some examples, R_9 is cycloalkylsulfonyl$_{(C\leq12)}$, such as cyclopropylsulfonyl$_{(C\leq12)}$.

In some examples, R_9 is $-CO_2R_{10}$, wherein R_{10} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$, or a substituted version of any of these groups. In some examples, R_{10} is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$. In further examples, R_{10} is

alkyl$_{(C\leq12)}$, such as methyl or *t*-butyl. In other examples, R_9 is $-C(O)R_{12}$, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups.

In some examples, R_{12} is hydrogen. In other examples, R_{12} is amino. In still other examples, R_{12} is $alkylamino_{(C\leq12)}$ or substituted $alkylamino_{(C\leq12)}$. In further examples, R_{12} is $alkylamino_{(C\leq12)}$, such as methylamino or ethylamino. In some examples, R_{12} is $dialkylamino_{(C\leq12)}$ or substituted $dialkylamino_{(C\leq12)}$. In other examples, R_{12} is $cycloalkylamino_{(C\leq12)}$ or substituted $cycloalkylamino_{(C\leq12)}$. In further examples, R_{12} is $cycloalkylamino_{(C\leq12)}$, such as cyclopropylamino. In some examples, R_{12} is $heterocycloalkyl_{(C\leq12)}$ or substituted $heterocycloalkyl_{(C\leq12)}$. In further examples, R_{12} is $heterocycloalkyl_{(C\leq12)}$, such as azetidine.

In some examples, Y is: $-CH=NOR_{11}$, wherein:

R_{11} is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$.

In some examples, R_{11} is hydrogen. In other examples, R_{11} is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$. In further examples, R_{11} is $alkyl_{(C\leq12)}$, such as methyl.

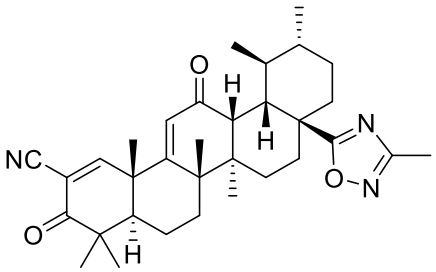
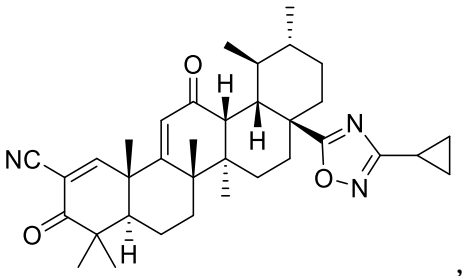
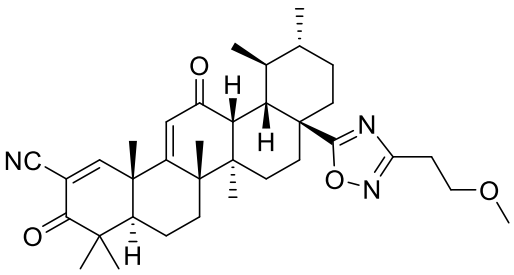
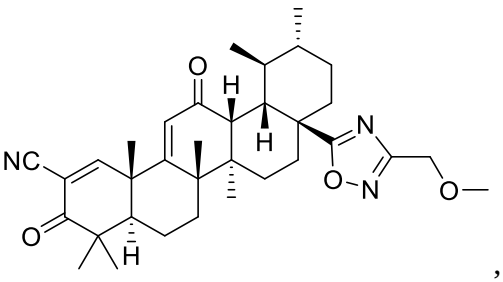
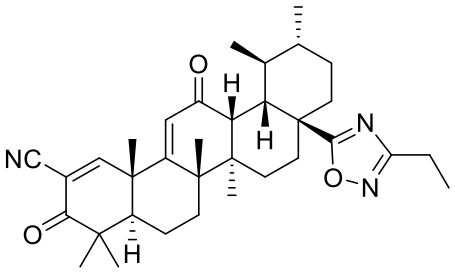
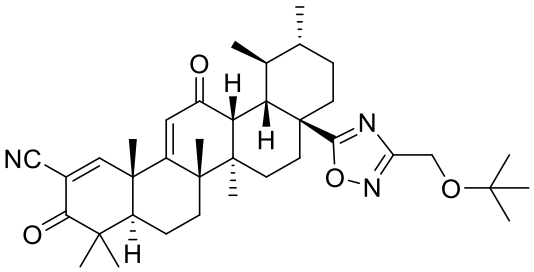
In some examples, Y is taken together with R_2 and is $-(CH_2)_mX_1-$, wherein:

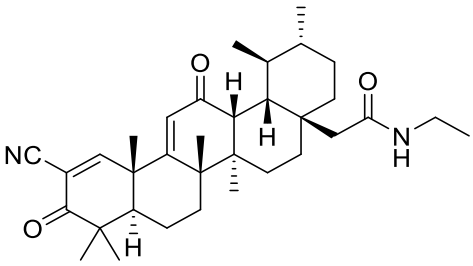
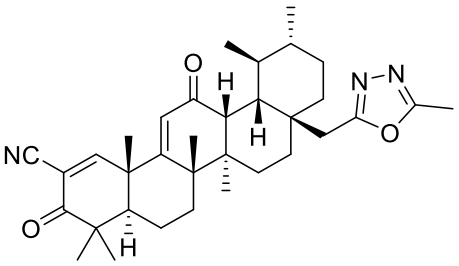
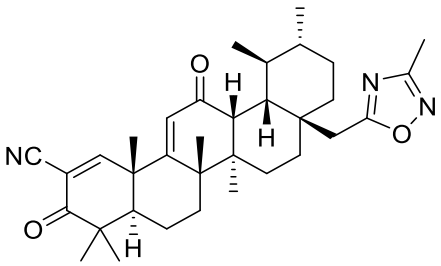
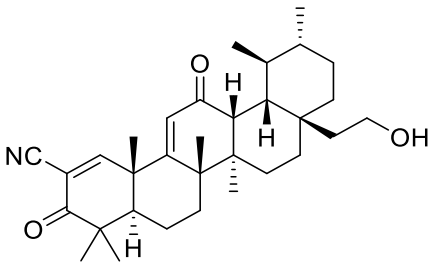
m is 0–6 and X_1 is $-O-$. In some examples, m is 1. In other examples, m is 2.

In some examples, Y is taken together with X_2 and is $-(CH_2)_oC(O)-$, wherein:

o is 0–6. In further examples, o is 1.

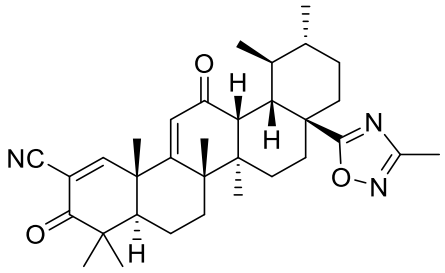
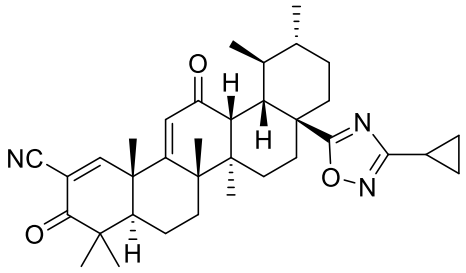
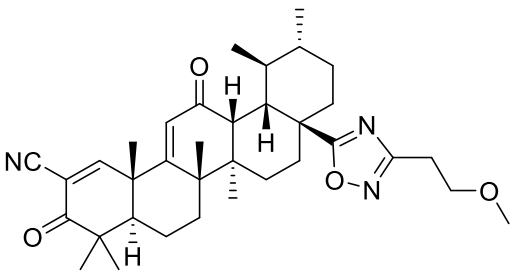
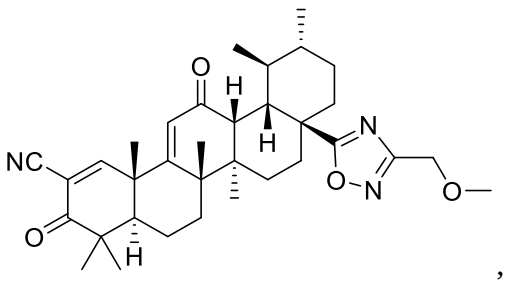
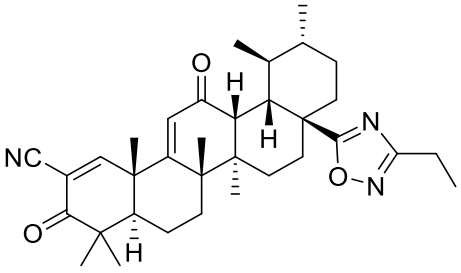
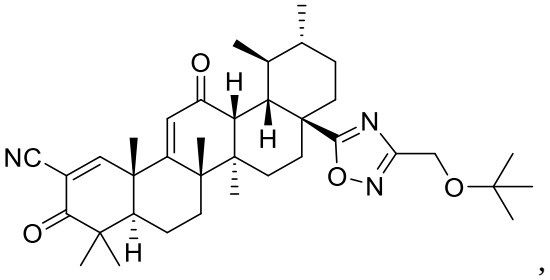
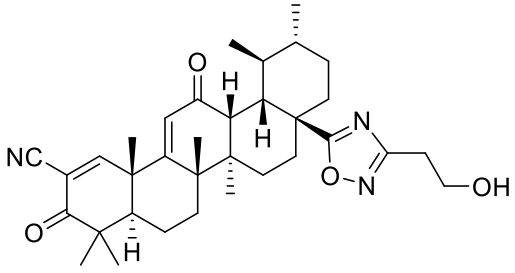
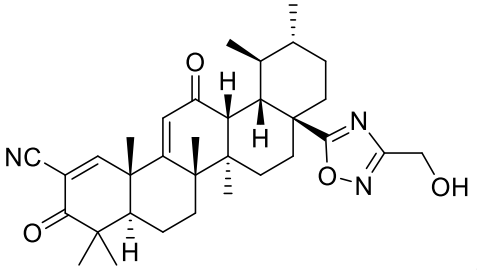
In some examples, the compound is further defined as


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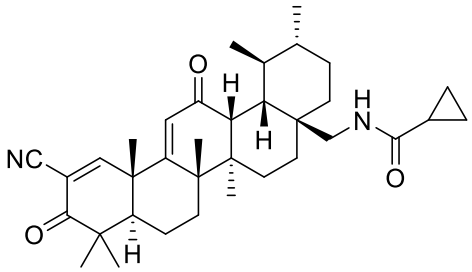
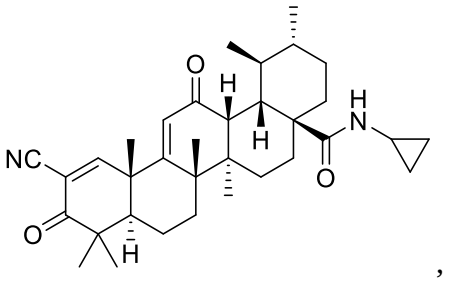
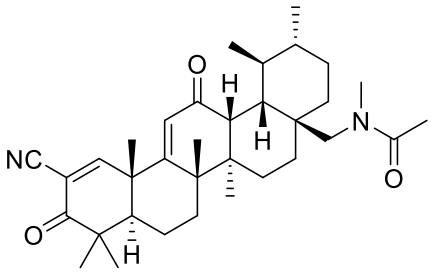
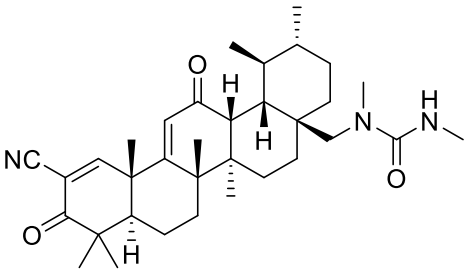
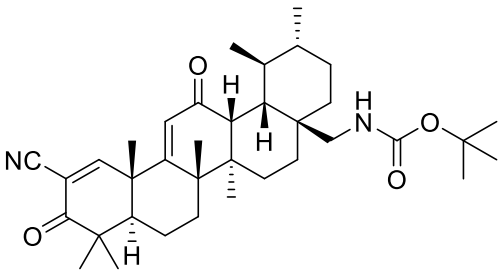
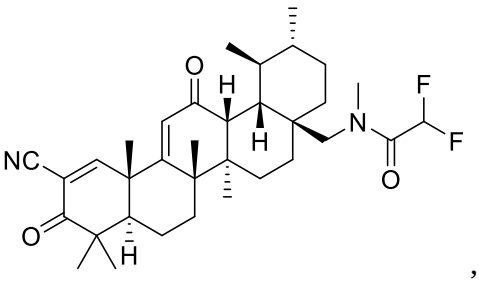
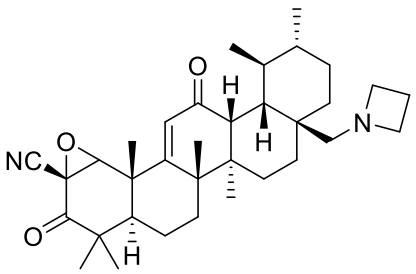
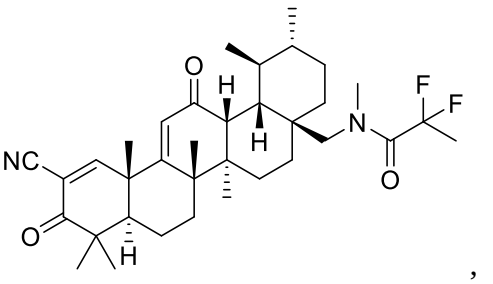
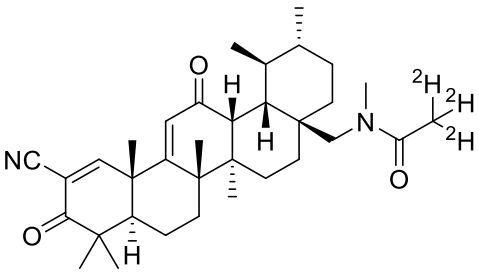
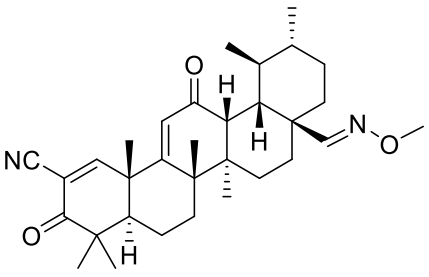

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or a pharmaceutically acceptable salt thereof.

In further examples, the compound is further defined as:


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In further examples, the compound is further defined as:


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or a pharmaceutically acceptable salt thereof.

In some examples, the compound is further defined as:

(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-4,4,6a,6b,11,12,14b-heptamethyl-8a-(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

2-((1S,2R,4aR,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-1,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)-N-ethylacetamide

(4aR,6aS,6bR,8aR,11R,12S,12aS,12bR,14bS)-4,4,6a,6b,11,12,14b-heptamethyl-8a-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile

(4aR,6aS,6bR,8aR,11R,12S,12aS,12bR,14bS)-4,4,6a,6b,11,12,14b-heptamethyl-8a-((3-methyl-1,2,4-oxadiazol-5-yl)methyl)-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile

(4aR,6aS,6bR,8aR,11R,12S,12aS,12bR,14bS)-8a-(2-hydroxyethyl)-4,4,6a,6b,11,12,14b-heptamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile

or a pharmaceutically acceptable salt thereof.

or a pharmaceutically acceptable salt thereof.

In some examples, the compound is further defined as:

(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-4,4,6a,6b,11,12,14b-heptamethyl-8a-(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-8a-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-4,4,6a,6b,11,12,14b-heptamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-8a-(3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl)-4,4,6a,6b,11,12,14b-heptamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-8a-(3-(methoxymethyl)-1,2,4-oxadiazol-5-yl)-4,4,6a,6b,11,12,14b-heptamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

N-((1S,2R,4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-1,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)-2,2-difluoropropanamide;

N-((1S,2R,4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-1,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)acetamide;

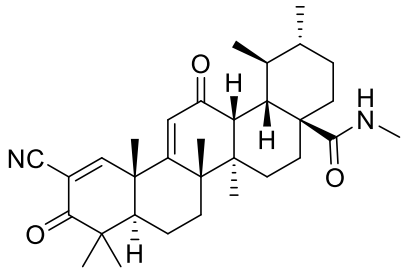
(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-8a-(hydroxymethyl)-4,4,6a,6b,11,12,14b-heptamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-4,4,6a,6b,11,12,14b-heptamethyl-3,13-dioxo-8a-((2-oxoazetidin-1-yl)methyl)-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile; or

(4aR,6aS,6bR,8aS,11R,12S,12aS,12bR,14bS)-4,4,6a,6b,11,12,14b-heptamethyl-3,13-dioxo-8a-((2-oxopyrrolidin-1-yl)methyl)-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

or a pharmaceutically acceptable salt thereof.

In one example, the compound is further defined as:



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or a pharmaceutically acceptable salt thereof.

In a further example, the compound is further defined as:

(1S,2R,4aS,6aR,6bS,8aR,12aS,14aR,14bS)-11-cyano-N,1,2,6a,6b,9,9,12a-octamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxamide

or a pharmaceutically acceptable salt thereof.

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

(A) a compound of the present disclosure; and

(B) an excipient.

In some examples, the pharmaceutical composition is formulated for administration orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion. In some examples, the pharmaceutical composition is formulated for oral administration. In some examples, the pharmaceutical composition is formulated for administration via injection. In some examples, the pharmaceutical composition is formulated for intraarterial administration, intramuscular administration, intraperitoneal administration, or intravenous administration. In some examples, the pharmaceutical composition is formulated for administration topically. In some examples, the pharmaceutical composition is formulated for topical administration to the skin or to the eye. In some examples, the pharmaceutical composition is formulated as a unit dose.

In still another example, the present disclosure provides methods of treating or preventing a disease or disorder in a patient in need thereof comprising administering to the patient a pharmaceutically effective amount of a compound or composition of the present disclosure. In some examples, the patient is a mammal, such as a human. In some examples, the disease or disorder is a condition associated with inflammation and/or oxidative stress. In some examples, the disease or disorder is cancer. In some examples, the disease or disorder is a cardiovascular disease, such as atherosclerosis. In some examples, the disease or disorder is an autoimmune disease, such as Crohn's disease, rheumatoid arthritis, lupus, or psoriasis. In some examples, the disease or disorder is a neurodegenerative disease, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease. In some examples, disease or disorder is chronic kidney disease, diabetes, mucositis, inflammatory bowel disease, dermatitis, sepsis, ischemia-reperfusion injury (including complications from sickle cell anemia), influenza, osteoarthritis, osteoporosis, pancreatitis, asthma, chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, multiple sclerosis, muscular dystrophy, cachexia, or graft-versus-host disease. In some examples, the disease or disorder is an eye disease, such as uveitis, glaucoma, macular degeneration, or retinopathy. In some examples, the disease or disorder is neuropsychiatric, such as schizophrenia, depression,

bipolar disorder, epilepsy, post-traumatic stress disorder, attention deficit disorder, autism, or anorexia nervosa. In some examples, the disease or disorder is associated with mitochondrial dysfunction, such as Friedreich's ataxia. In some examples, the disease or disorder is chronic pain. In some examples, the disease or disorder is neuropathic pain.

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

In another aspect, there is provided the compound or pharmaceutical composition as defined above for use in treatment or prevention of a disease or disorder in a patient.

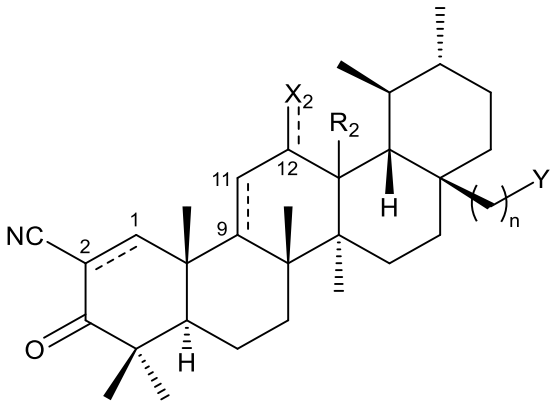
In another aspect, there is provided the use of a compound or pharmaceutical composition as defined above in the manufacture of a medicament for the treatment or prevention of a disease or disorder in a patient.

In another aspect, there is provided the use of the compound or pharmaceutical composition as defined above in the manufacture of a medicament for the inhibition of nitric oxide production in one or more cells of a patient.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples of the disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure 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.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(I-A),

wherein:

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

the bond between atom 9 and atom 11 is a single bond or a double bond;

the bond between atom 12 and X_2 is a single bond or a double bond;

n is 0–6;

X_2 is oxo, or X_2 is taken together with Y as defined below, provided that when X_2 is oxo, then the bond between atom 12 and X_2 is a double bond, and when X_2 is taken together with Y as defined below, that the bond between atom 12 and X_2 is a single bond;

R_2 is hydrogen or hydroxy; or R_2 is taken together with Y as defined below; and

Y is hydrogen, hydroxy, halo, or amino; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

$-arenediyl_{(C\leq12)}-R_3$, substituted $-arenediyl_{(C\leq12)}-R_3$,

$-heteroarenediyl_{(C\leq12)}-R_3$, or substituted $-heteroarenediyl_{(C\leq12)}-R_3$,

wherein:

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

$-alkanediyl_{(C\leq12)}-R_4$ or substituted $-alkanediyl_{(C\leq12)}-R_4$,

wherein:

R_4 is alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, or a substituted version of any of these groups; or

−alkanediyl$_{(C\leq12)}$−C(O)R_5, or substituted −alkanediyl$_{(C\leq12)}$−C(O)R_5, wherein:

R_5 is hydroxy or amino; or

alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups;

−C(O)R_7, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, substituted heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, substituted cycloalkylamino$_{(C\leq12)}$, -NHC(NH)-alkyl$_{(C\leq12)}$, or -NHOR$_{13}$, wherein:

R_{13} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$;

−NR_8R_9, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$, or

−CO_2R_{10}, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−C(O)R_{12}, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−CH=NOR_{11}, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; or

Y is taken together with R_2 and is −$(CH_2)_mX_1$−, wherein:

m is 0–6; and

X_1 is −O−; or

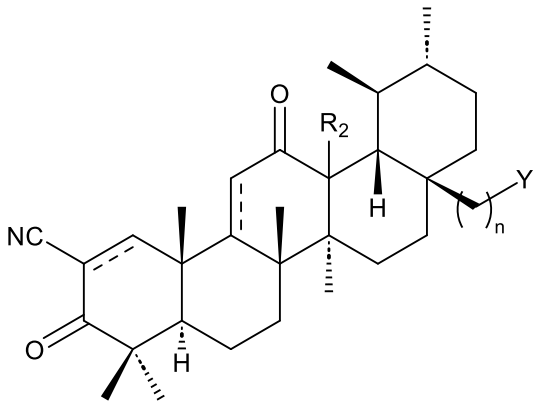
Y is taken together with X_2 and is −$(CH_2)_o$C(O)−, wherein:

o is 0-6; and

X_2 is −O−;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein the compound is further defined as:



(I),

wherein:

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

the bond between atom 9 and atom 11 is a single bond or a double bond;

n is 0–6;

R_2 is hydrogen or hydroxy; or R_2 is taken together with Y as defined below; and

Y is hydrogen, hydroxy, halo, or amino; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, or a substituted version of any of these groups;

$-arenediyl_{(C\leq12)}-R_3$, substituted $-arenediyl_{(C\leq12)}-R_3$,

$-heteroarenediyl_{(C\leq12)}-R_3$, or substituted $-heteroarenediyl_{(C\leq12)}-R_3$,

wherein:

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

$-alkanediyl_{(C\leq12)}-R_4$ or substituted $-alkanediyl_{(C\leq12)}-R_4$, wherein:

R_4 is $alkoxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of any of these groups; or

$-alkanediyl_{(C\leq12)}-C(O)R_5$ or substituted $-alkanediyl_{(C\leq12)}-C(O)R_5$,

wherein:

R_5 is hydroxy or amino; or

alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-C(O)R_7$, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, substituted heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, substituted cycloalkylamino$_{(C\leq12)}$, $-NHC(NH)$-alkyl$_{(C\leq12)}$, or $-NHOR_{13}$, wherein:

R_{13} is hydrogen, alkyl, or substituted alkyl;

$-NR_8R_9$, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$,

$-CO_2R_{10}$, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-C(O)R_{12}$, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$ or a substituted version of any of these groups;

$-CH=NOR_{11}$, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; or

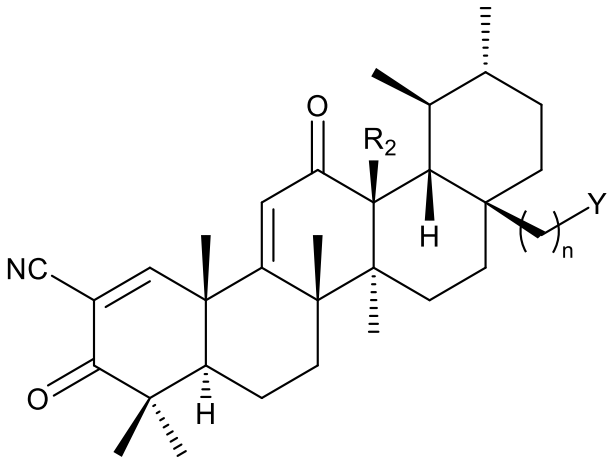
Y is taken together with R_2 and is $-(CH_2)_mX_1-$, wherein:

m is 0–6; and

X_1 is $-O-$;

or a pharmaceutically acceptable salt thereof.

3. The compound of either claim 1 or claim 2, wherein the compound is further defined as:



(II),

wherein:

n is 0–6;

R_2 is hydrogen or hydroxy; or R_2 is taken together with Y as defined below; and

Y is hydrogen, hydroxy, halo, or amino; or

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−arenediyl$_{(C\leq12)}$−R_3, substituted −arenediyl$_{(C\leq12)}$−R_3, −heteroarenediyl$_{(C\leq12)}$−R_3, or substituted −heteroarenediyl$_{(C\leq12)}$−R_3, wherein:

R_3 is alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−alkanediyl$_{(C\leq12)}$−R_4 or substituted −alkanediyl$_{(C\leq12)}$−R_4, wherein:

R_4 is alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, or a substituted version of any of these groups; or

−alkanediyl$_{(C\leq12)}$−C(O)R_5 or substituted −alkanediyl$_{(C\leq12)}$−C(O)R_5, wherein:

R_5 is hydroxy or amino; or

alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−C(O)R_7, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, substituted heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, substituted cycloalkylamino$_{(C\leq12)}$, -NHC(NH)-alkyl$_{(C\leq12)}$, or -NHOR_{13}, wherein:

R_{13} is hydrogen, alkyl, or substituted alkyl;

−NR_8R_9, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$,

−CO_2R_{10}, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−C(O)R_{12}, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$ or a substituted version of any of these groups;

−CH=NOR_{11}, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; or

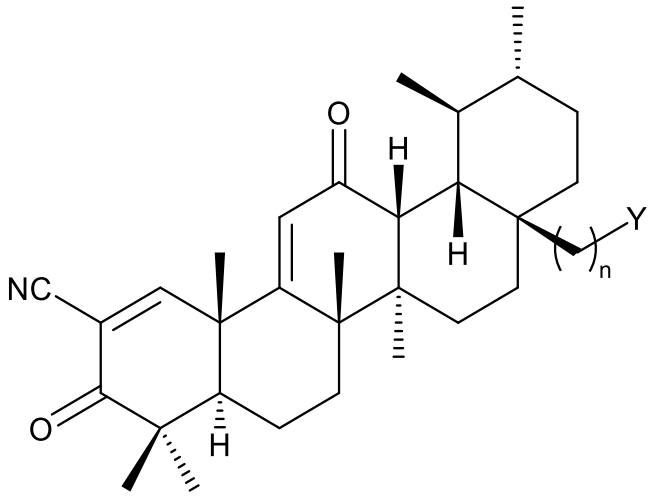
Y is taken together with R_2 and is −$(CH_2)_mX_1$−, wherein:

m is 0–6; and

X_1 is −O−;

or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3, wherein the compound is further defined as:



(III),

wherein:

n is 0–6;

Y is hydrogen, hydroxy, halo, or amino; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, or a substituted version of any of these groups; or

$-arenediyl_{(C\leq12)}-R_3$, substituted $-arenediyl_{(C\leq12)}-R_3$, $-heteroarenediyl_{(C\leq12)}-R_3$, or substituted $-heteroarenediyl_{(C\leq12)}-R_3$, wherein:

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

$-alkanediyl_{(C\leq12)}-R_4$ or substituted $-alkanediyl_{(C\leq12)}-R_4$, wherein:

R_4 is $alkoxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, or a substituted version of any of these groups; or

$-alkanediyl_{(C\leq12)}-C(O)R_5$ or substituted $-alkanediyl_{(C\leq12)}-C(O)R_5$, wherein:

R_5 is hydroxy or amino; or

$alkoxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, or a substituted version of any of these groups; or

−C(O)R_7, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, substituted heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, substituted cycloalkylamino$_{(C\leq12)}$, −NHC(NH) −alkyl$_{(C\leq12)}$, or −NHOR_{13}, wherein:

R_{13} is hydrogen, alkyl, or substituted alkyl;

−NR_8R_9, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$,

−CO_2R_{10}, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

−C(O)R_{12}, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$ or a substituted version of any of these groups;

−CH=NOR_{11}, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1-4, wherein n is 0, 1, or 2.

6. The compound according to any one of claims 1-5, wherein n is 0.

7. The compound according to any one of claims 1-5, wherein n is 1.

8. The compound according to any one of claims 1-5, wherein n is 2.

9. The compound according to any one of claims 1-8, wherein Y is hydroxy, halo, or amino.

10. The compound according to any one of claims 1-8, wherein Y is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$.

11. The compound according to any one of claims 1-8 and 10, wherein Y is substituted alkyl$_{(C\leq12)}$.

12. The compound according to any one of claims 1-8, 10, and 11, wherein Y is hydroxymethyl or methylaminomethyl.

13. The compound according to any one of claims 1-8, wherein Y is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12)}$.

14. The compound according to any one of claims 1-8 and 13, wherein Y is substituted heterocycloalkyl$_{(C\leq12)}$.

15. The compound according to any one of claims 1-8, 13, and 14, wherein Y is selected from the group of: 2-oxooxazolidin-3-yl, 3-methyl-2-oxoimidazolidin-1-yl, 2-oxoimidazolidin-1-yl, 2,5-dioxopyrrolidin-1-yl, methyl 3-oxopyrazolidine-1-carboxylate, 5-oxopyrazolidin-1-yl, 2-oxoazetidin-1-yl and 2-oxopyrrolidin-1-yl.

16. The compound according to any one of claims 1-8, wherein Y is heteroaryl$_{(C\leq12)}$ or substituted heteroaryl$_{(C\leq12)}$.

17. The compound according to any one of claims 1-8 and 16, wherein Y is heteroaryl$_{(C\leq12)}$.

18. The compound according to any one of claims 1-8, 16, and 17, wherein Y is 3-methyl-1,2,4-oxadiazol-5-yl, 3-ethyl-1,2,4-oxadiazol-5-yl, 1H-pyrazol-1-yl, 1H-1,2,4-triazol-1-yl, 4-methyl-1H-1,2,3-triazol-1-yl, 1H-tetrazol-1-yl, 1H-1,2,3-triazol-1-yl, 1H-imidazol-1-yl, 5-methyl-1,3,4-oxadiazol-2-yl, or 5-methyl-1,2,4-oxadiazol-3-yl.

19. The compound according to any one of claims 1-8 and 16, wherein Y is substituted heteroaryl$_{(C\leq12)}$.

20. The compound according to any one of claims 1-8, 16, and 19, wherein Y is 4-bromo-1H-pyrazol-1-yl, 3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl, 3-(methoxymethyl)-1,2,4-oxadiazol-5-yl, 3-(2-hydroxyethyl)-1,2,4-oxadiazol-5-yl, 3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl, 3-((dimethylamino)methyl)-1,2,4-oxadiazol-5-yl, 3-(1-methoxyethyl)-1,2,4-oxadiazol-5-yl, or 3-(fluoromethyl)-1,2,4-oxadiazol-5-yl.

21. The compound according to any one of claims 1-8, wherein Y is −alkanediyl$_{(C\leq12)}$ −C(O)R_5 or substituted −alkanediyl$_{(C\leq12)}$−C(O)R_5, wherein:

R_5 is hydroxy or amino; or

alkoxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, cycloalkoxy$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups.

22. The compound according to any one of claims 1-8 and 21, wherein R_5 is hydroxy.

23. The compound according to any one of claims 1-8 and 21, wherein R_5 is amino.

24. The compound according to any one of claims 1-8 and 21, wherein R_5 is alkylamino$_{(C\leq12)}$.

25. The compound according to any one of claims 1-8, 21, and 24, wherein R_5 is methylamino or ethylamino.

26. The compound according to any one of claims 1-8 and 21, wherein R_5 is cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$.

27. The compound according to any one of claims 1-8, 21, and 26, wherein R_5 is cycloalkylamino$_{(C\leq12)}$.

28. The compound according to any one of claims 1-8, 21, 26, and 27, wherein R_5 is cyclopropylamino.

29. The compound according to any one of claims 1-8 and 21, wherein R_5 is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12)}$.

30. The compound according to any one of claims 1-8, 21, and 29, wherein R_5 is heterocycloalkyl$_{(C\leq12)}$.

31. The compound according to any one of claims 1-8, 21, 29, and 30, wherein R_5 is azetidine or pyrrolidine.

32. The compound according to any one of claims 1-8, wherein Y is:

$-C(O)R_7$, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$, $-NHC(NH)-$alkyl$_{(C\leq12)}$, or $-NHOR_{13}$, wherein:

R_{13} is hydrogen, alkyl, or substituted alkyl;

$-NR_8R_9$, wherein:

R_8 is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$; and

R_9 is acyl$_{(C\leq12)}$, substituted acyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, substituted cycloalkylsulfonyl$_{(C\leq12)}$, or

$-CO_2R_{10}$, wherein:

R_{10} is hydrogen, alkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-C(O)R_{12}$, wherein:

R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups; or

$-CH=NOR_{11}$, wherein:

R_{11} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$.

33. The compound according to any one of claims 1-8 and 32, wherein Y is:

$-C(O)R_7$, wherein:

R_7 is hydrogen, heterocycloalkyl$_{(C\leq12)}$, substituted heterocycloalkyl$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$, $-NHC(NH)-$alkyl$_{(C\leq12)}$, or $-NHOR_{13(C\leq12)}$, wherein:

R_{13} is hydrogen, alkyl, or substituted alkyl.

34. The compound according to any one of claims 1-8, 32, and 33, wherein R_7 is hydrogen.

35. The compound according to any one of claims 1-8, 32, and 33, wherein R_7 is cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$.

36. The compound according to any one of claims 1-8, 32, 33, and 35, wherein R_7 is cycloalkylamino$_{(C\leq12)}$.

37. The compound according to any one of claims 1-8, 32, 33, 35, and 36, wherein R_7 is cyclopropylamino.

38. The compound according to any one of claims 1-8, 32, and 33, wherein R_7 is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12)}$.

39. The compound according to any one of claims 1-8, 32, 33, and 38, wherein R_7 is heterocycloalkyl$_{(C\leq12)}$.

40. The compound according to any one of claims 1-8, 32, 33, 38, and 39, wherein R_7 is azetidine or pyrrolidine.

41. The compound according to any one of claims 1-8 and 32, wherein Y is:

$-NR_8R_9$, wherein:

R_8 is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$; and

R_9 is $acyl_{(C\leq12)}$, substituted $acyl_{(C\leq12)}$, $alkylsulfonyl_{(C\leq12)}$, substituted $alkylsulfonyl_{(C\leq12)}$, $cycloalkylsulfonyl_{(C\leq12)}$, substituted $cycloalkylsulfonyl_{(C\leq12)}$; or $-CO_2R_{10}$, wherein R_{10} is hydrogen, $alkyl_{(C\leq12)}$, or substituted $alkyl_{(C\leq12)}$, or a substituted version of any of these groups; or $-C(O)R_{12}$, wherein:

R_{12} is hydrogen, amino, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $cycloalkylamino_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, or a substituted version of any of these groups.

42. The compound according to any one of claims 1-8, 32, and 41, wherein R_8 is hydrogen.

43. The compound according to any one of claims 1-8, 32, and 41, wherein R_8 is $alkyl_{(C\leq12)}$ or substituted $alkyl_{(C\leq12)}$.

44. The compound according to any one of claims 1-8, 32, 41, and 43, wherein R_8 is $alkyl_{(C\leq12)}$.

45. The compound according to any one of claims 1-8, 32, 41, 43, and 44, wherein R_8 is methyl.

46. The compound according to any one of claims 1-8, 32, and 41-45, wherein R_9 is $acyl_{(C\leq12)}$ or substituted $acyl_{(C\leq12)}$.

47. The compound according to any one of claims 1-8, 32, and 41-46, wherein R_9 is $acyl_{(C\leq12)}$.

48. The compound according to any one of claims 1-8, 32, and 41-47, wherein R_9 is acetyl, methylacetyl, cyclopropanecarboxyl, or cyclobutanecarboxyl.

49. The compound of claim 48, wherein R_9 is acetyl, further wherein the acetyl is substantially $-C(O)CD_3$.

50. The compound according to any one of claims 1-8, 32, and 41-46, wherein R_9 is substituted $acyl_{(C\leq12)}$.

51. The compound according to any one of claims 1-8, 32, 41-46, and 50, wherein R_9 is methylaminocarbonyl, difluoroacetyl, or difluoromethylacetyl.

52. The compound according to any one of claims 1-8, 32, and 41-45, wherein R_9 is alkylsulfonyl$_{(C\leq12)}$, substituted alkylsulfonyl$_{(C\leq12)}$, cycloalkylsulfonyl$_{(C\leq12)}$, or substituted cycloalkylsulfonyl$_{(C\leq12)}$.

53. The compound according to any one of claims 1-8, 32, 41-45, and 52, wherein R_9 is alkylsulfonyl$_{(C\leq12)}$.

54. The compound according to any one of claims 1-8, 32, 41-45, 49, and 53, wherein R_9 is methylsulfonyl or ethylsulfonyl.

55. The compound according to any one of claims 1-8, 32, 41-45, and 52, wherein R_9 is cycloalkylsulfonyl$_{(C\leq12)}$.

56. The compound according to any one of claims 1-8, 32, 41-45, 52, and 55, wherein R_9 is cyclopropylsulfonyl$_{(C\leq12)}$.

57. The compound according to any one of claims 1-8, 32, and 41-45, wherein R_9 is $-CO_2R_{10}$, wherein R_{10} is hydrogen, alkyl$_{(C\leq12)}$, or substituted alkyl$_{(C\leq12)}$, or a substituted version of any of these groups.

58. The compound according to any one of claims 1-8, 32, 41-45, and 57, wherein R_{10} is alkyl$_{(C\leq12)}$ or substituted alkyl$_{(C\leq12)}$.

59. The compound according to any one of claims 1-8, 32, 41-45, 57, and 58, wherein R_{10} is alkyl$_{(C\leq12)}$.

60. The compound according to any one of claims 1-8, 32, 41-45, and 57-59, wherein R_{10} is methyl or *t*-butyl.

61. The compound according to any one of claims 1-8, 32, and 41-45, wherein R_9 is $-C(O)R_{12}$, wherein:

    R_{12} is hydrogen, amino, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, cycloalkylamino$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, or a substituted version of any of these groups.

62. The compound according to any one of claims 1-8, 32, 41-45, and 61, wherein R_{12} is alkylamino$_{(C\leq12)}$ or substituted alkylamino$_{(C\leq12)}$.

63. The compound according to any one of claims 1-8, 32, 41-45, 61, and 62, wherein R_{12} is alkylamino$_{(C\leq12)}$.

64. The compound according to any one of claims 1-8, 32, 41-45, and 61-63, wherein R_{12} is methylamino or ethylamino.

65. The compound according to any one of claims 1-8, 32, 41-45, and 61, wherein R_{12} is cycloalkylamino$_{(C\leq12)}$ or substituted cycloalkylamino$_{(C\leq12)}$.

66. The compound according to any one of claims 1-8, 32, 41-45, 61, and 65, wherein R_{12} is cycloalkylamino$_{(C\leq12)}$

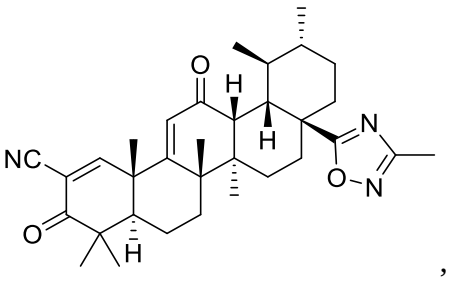
67. The compound according to any one of claims 1-8, 32, 41-45, 61, 65, and 66, wherein R_{12} is cyclopropylamino.

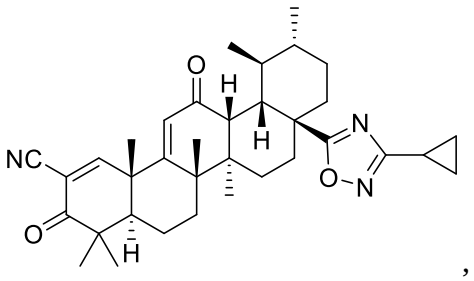
68. The compound according to any one of claims 1-8, 32, 41-45, and 61, wherein R_{12} is heterocycloalkyl$_{(C\leq12)}$ or substituted heterocycloalkyl$_{(C\leq12)}$.

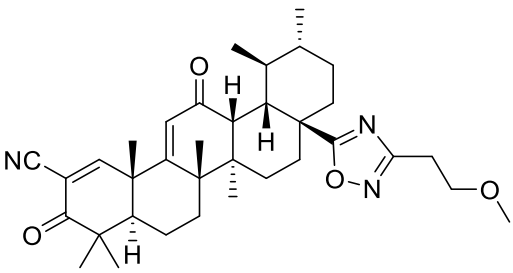
69. The compound according to any one of claims 1-8, 32, 41-45, 61, and 68, wherein R_{12} is heterocycloalkyl$_{(C\leq12)}$.

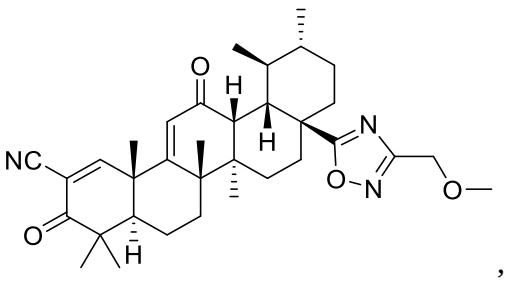
70. The compound according to any one of claims 1-8, 32, 41-45, 61, 68 and 69, wherein R_{12} is azetidine.

71. The compound according to any one of claims 1-70, wherein the compound is further defined as:

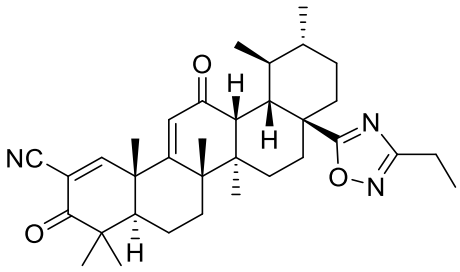
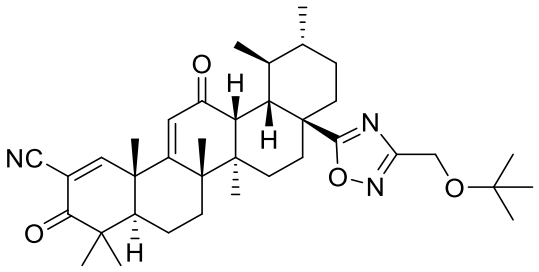
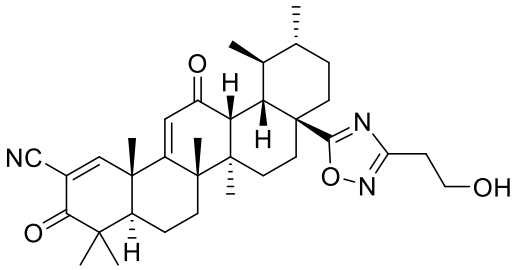
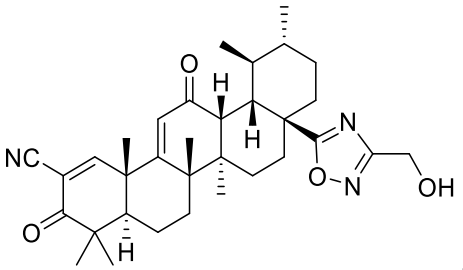
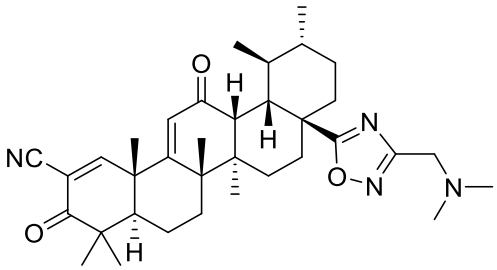
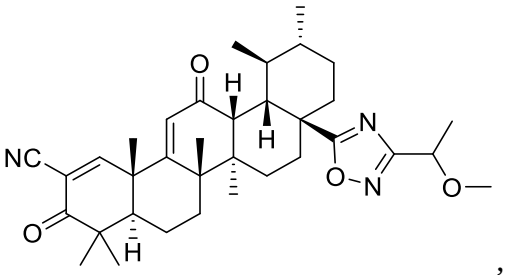
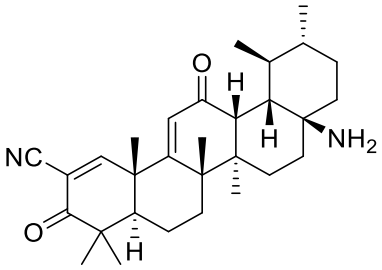
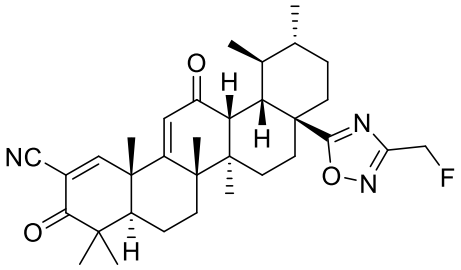
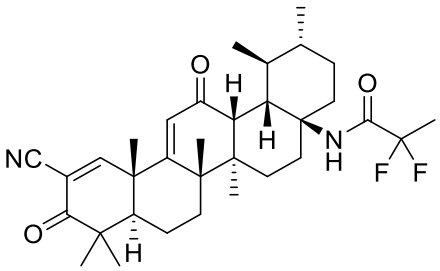
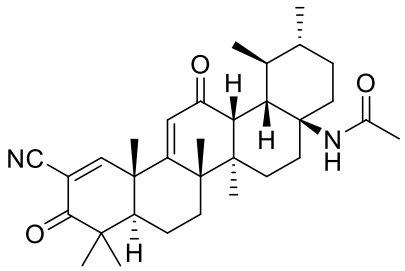
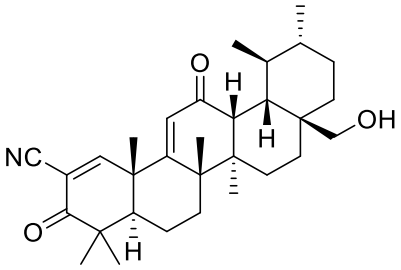
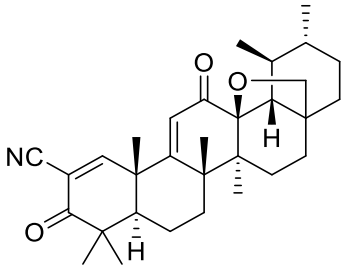
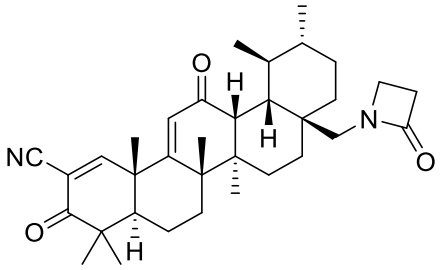


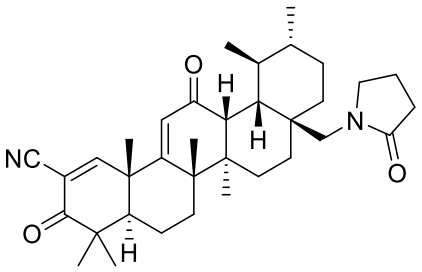
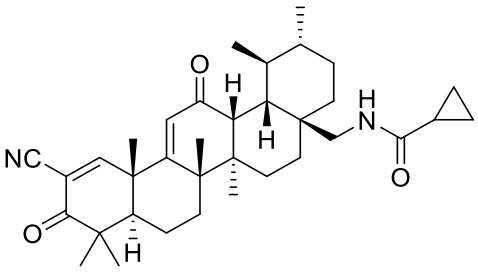
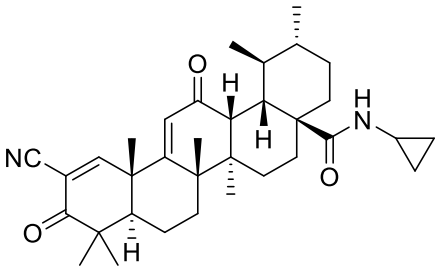
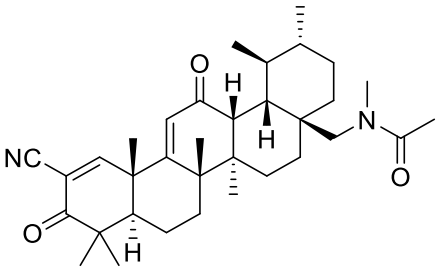
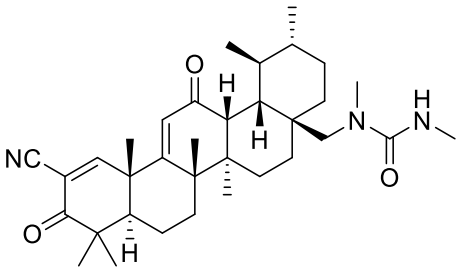
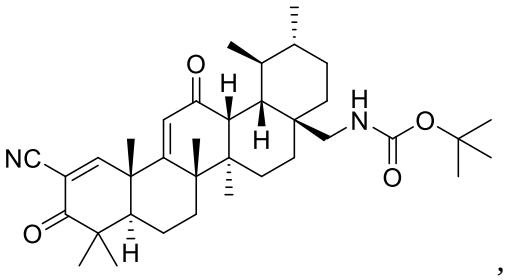
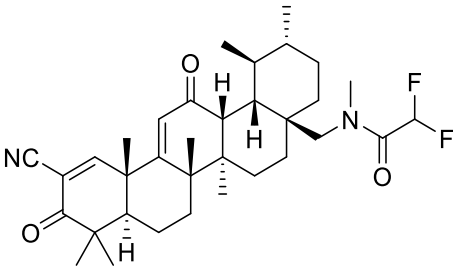
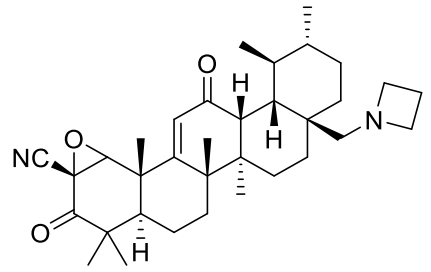
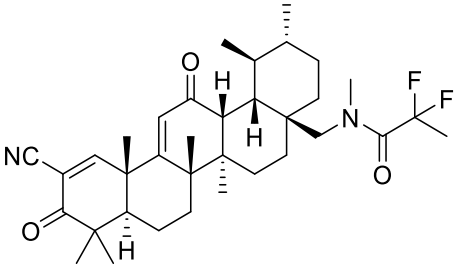
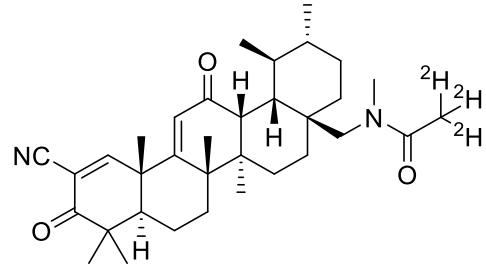
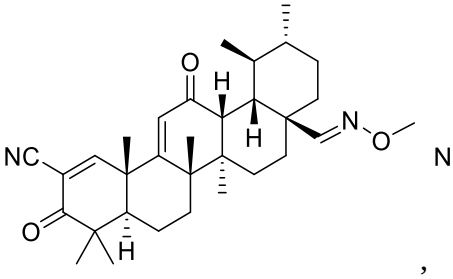
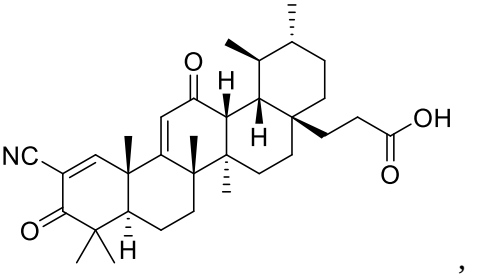
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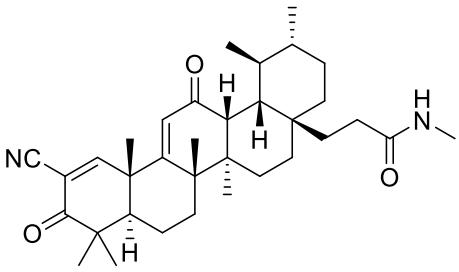
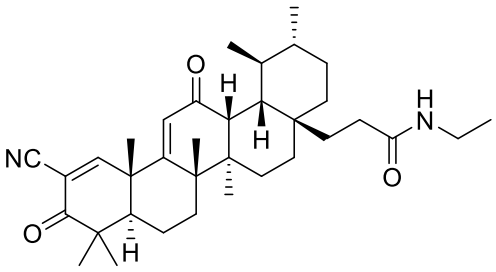
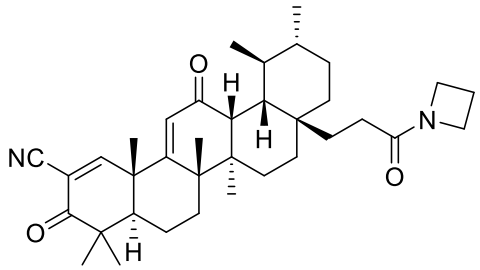
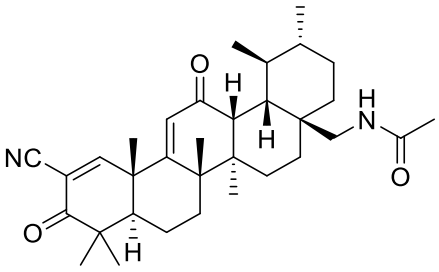
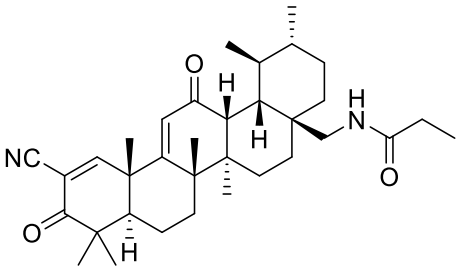
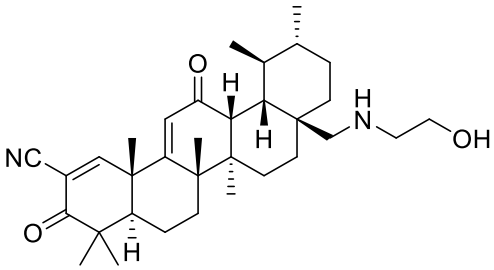
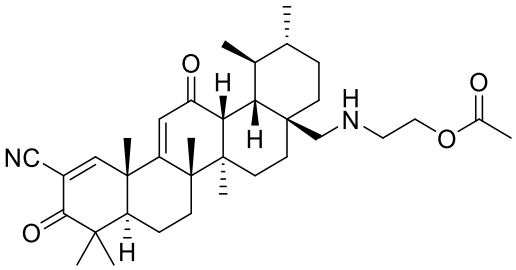
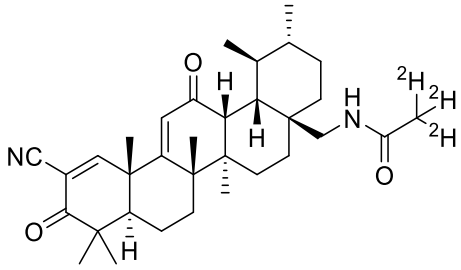
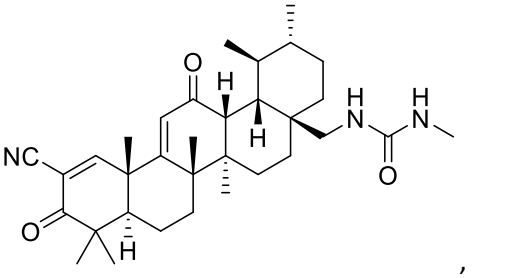
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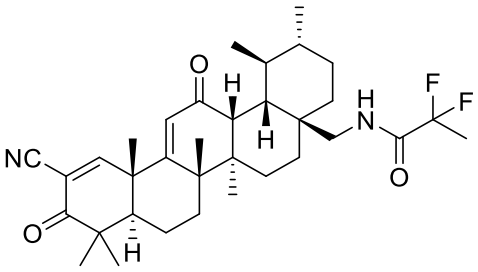
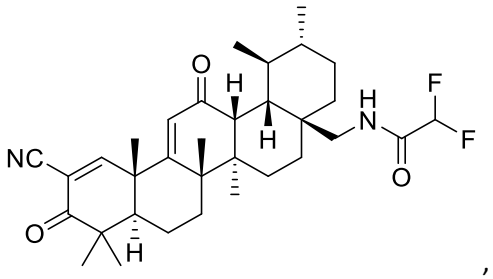
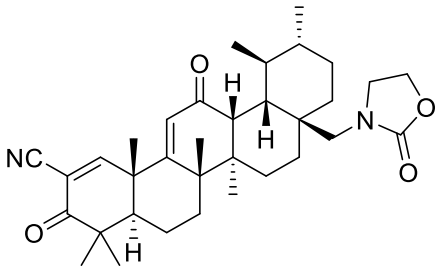
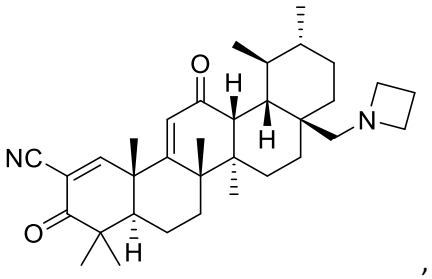
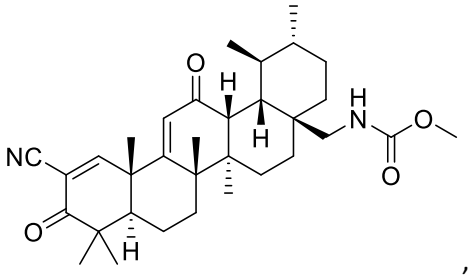
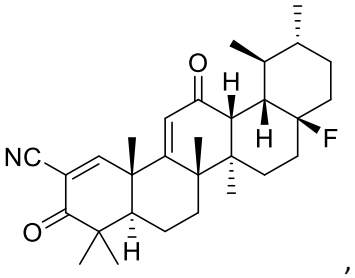
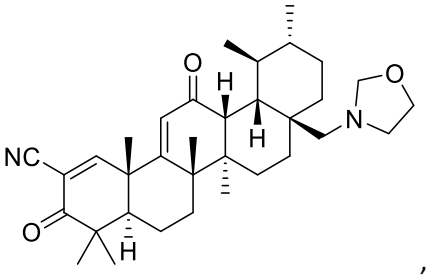
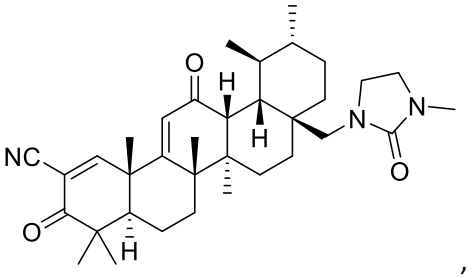
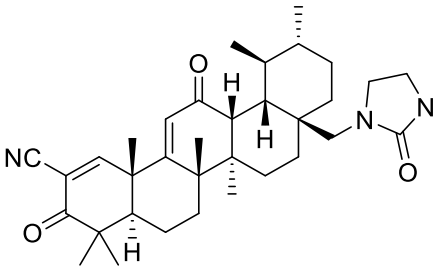
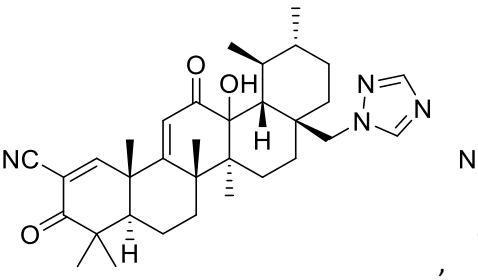
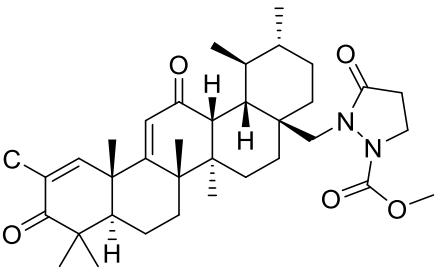

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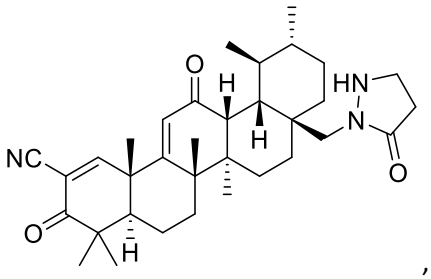
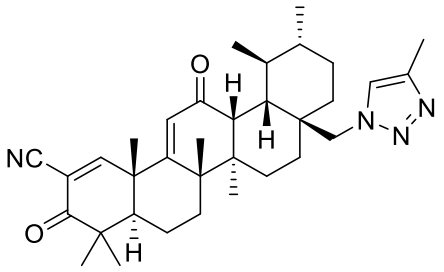
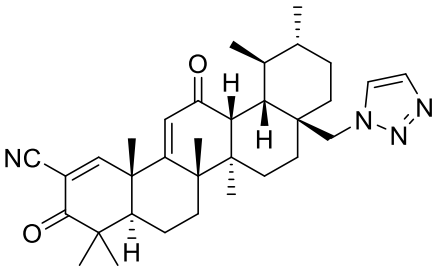
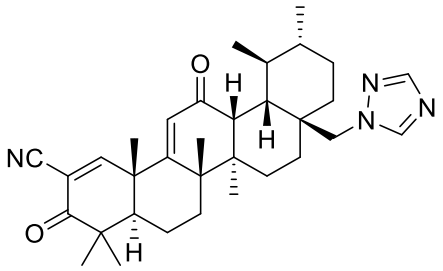
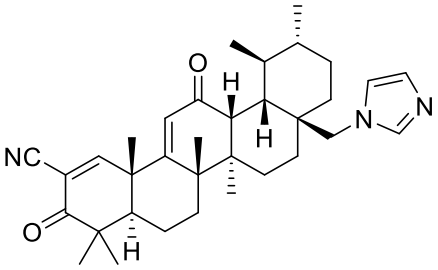
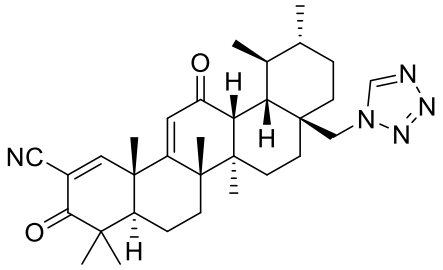
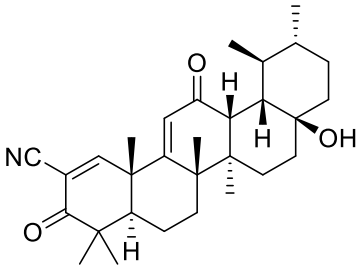
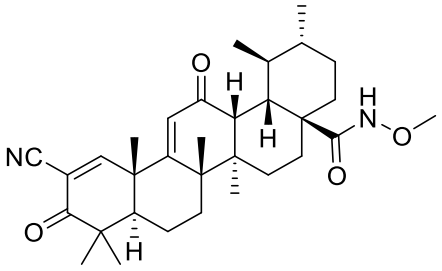
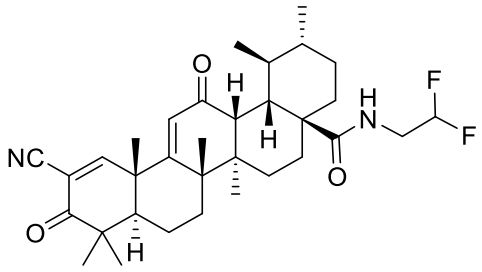
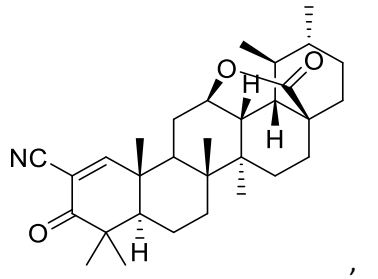
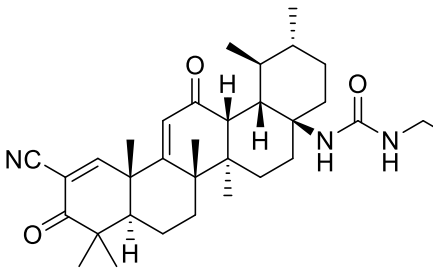
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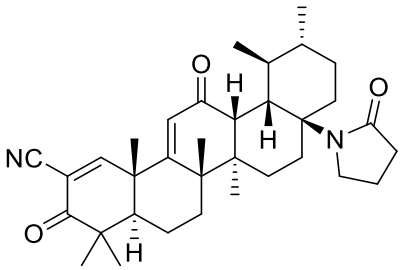
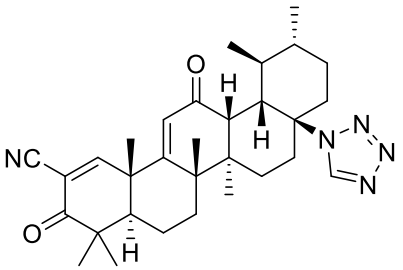
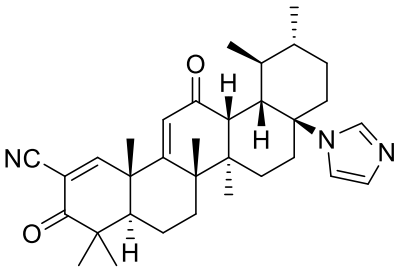
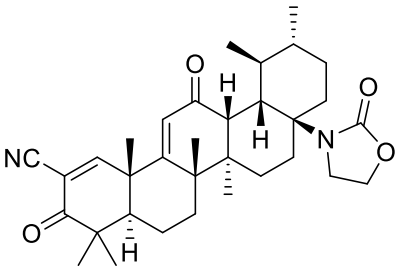
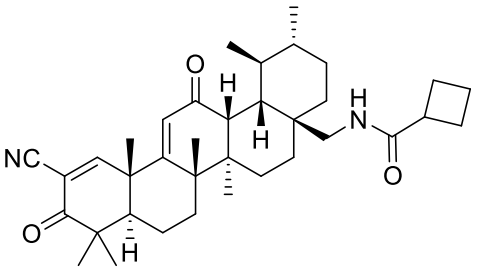
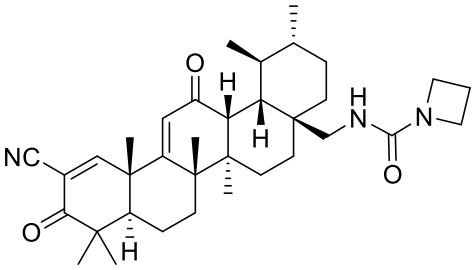
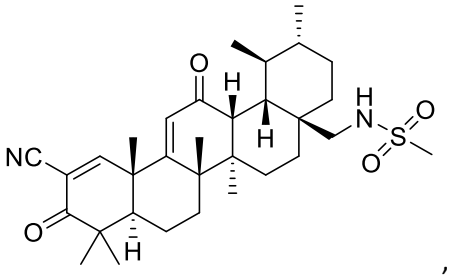
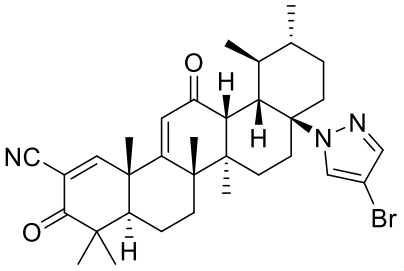
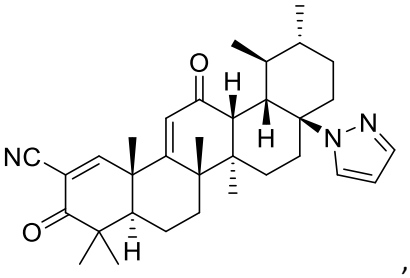
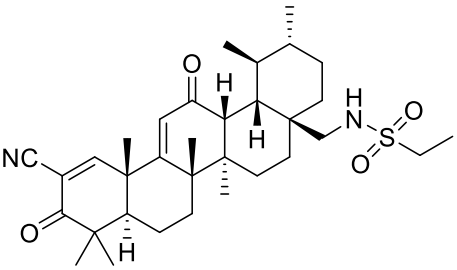
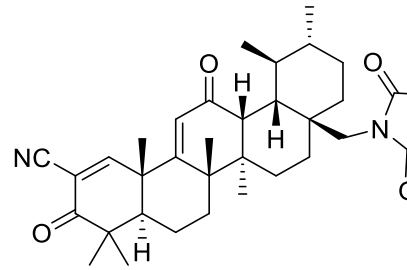
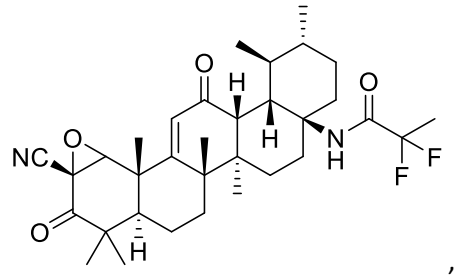
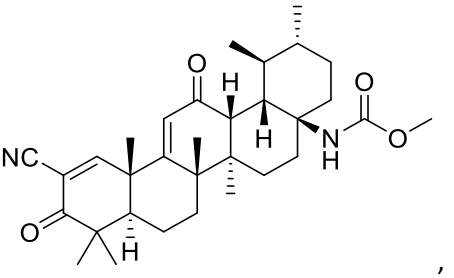

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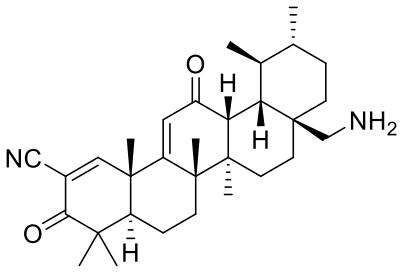
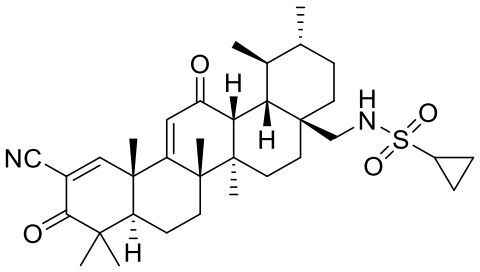
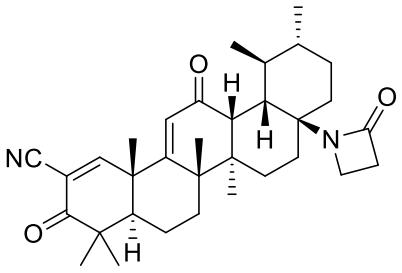
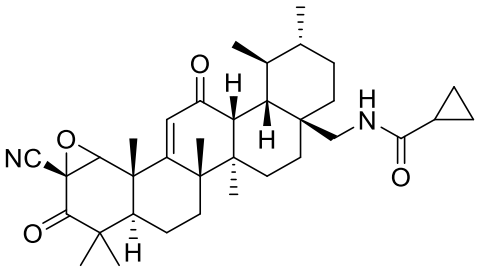
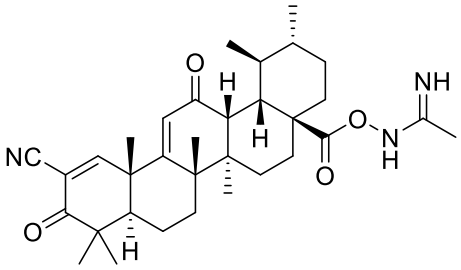
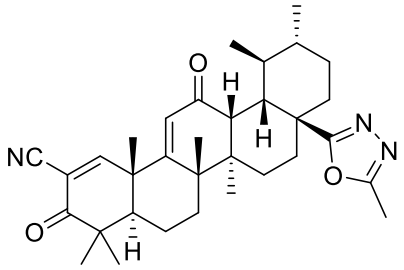
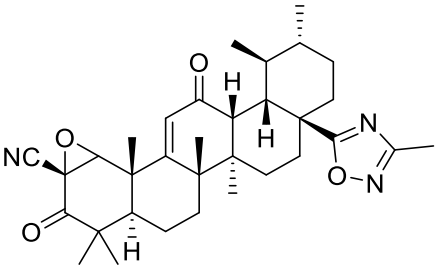
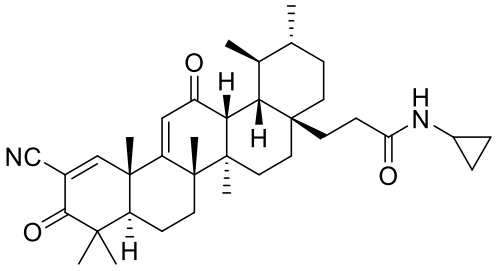
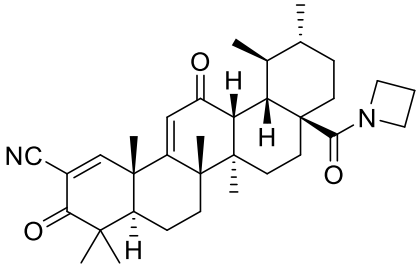
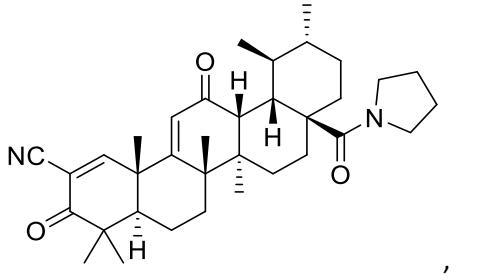
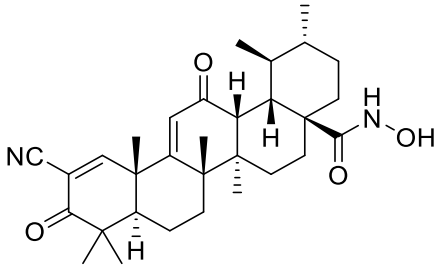
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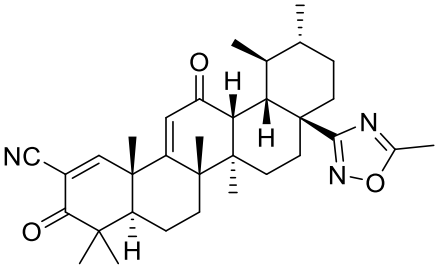
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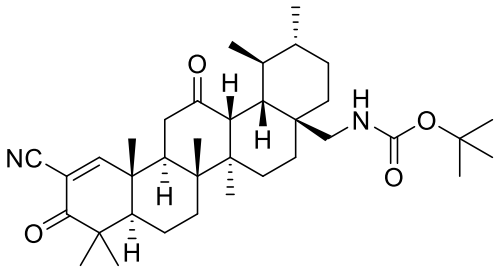
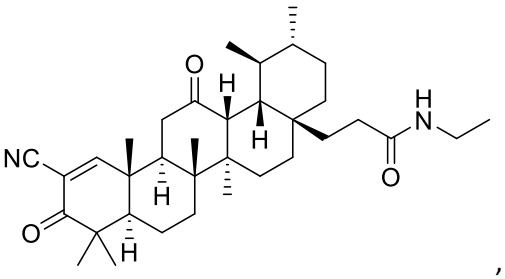
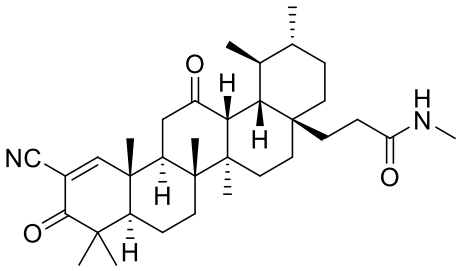
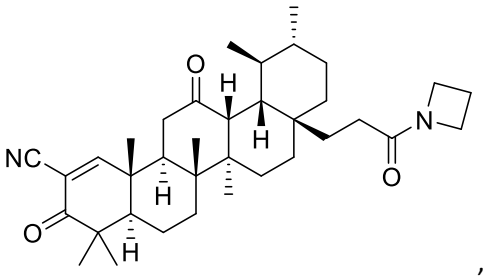
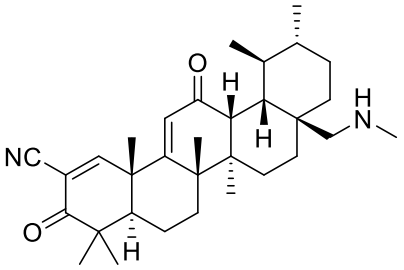
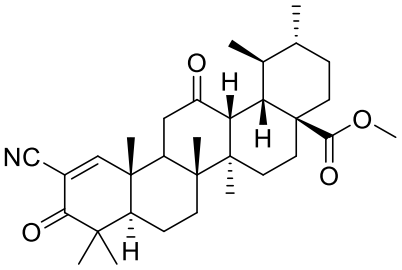
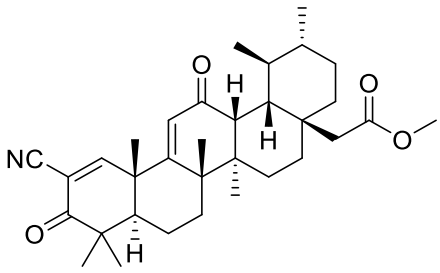
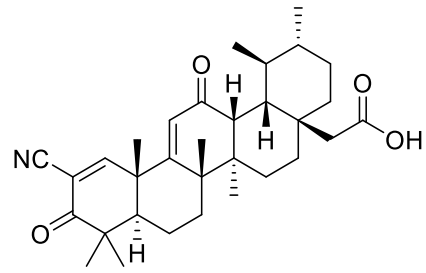
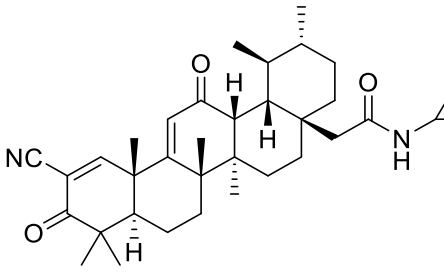
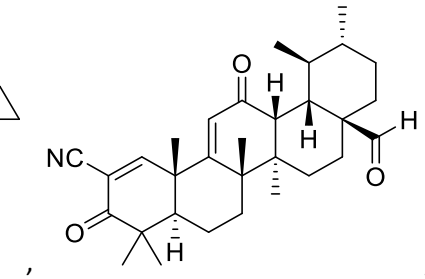
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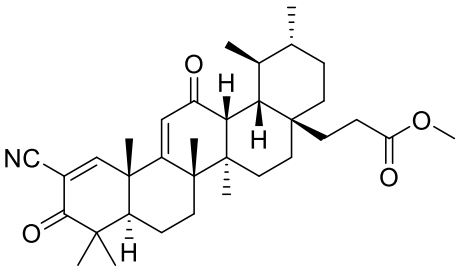
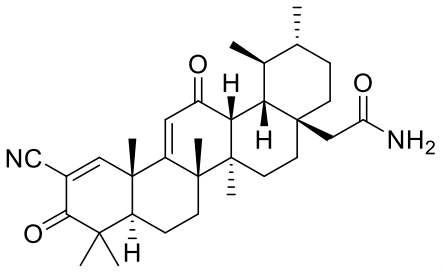
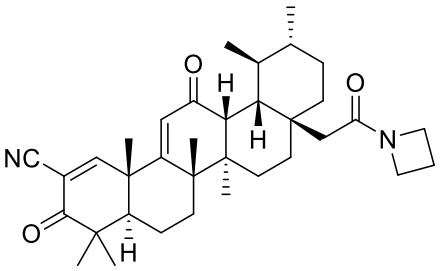
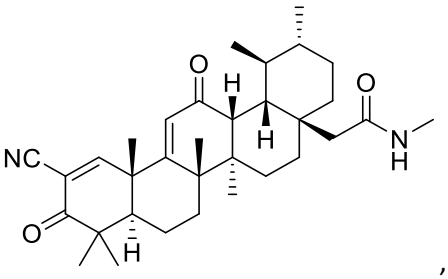
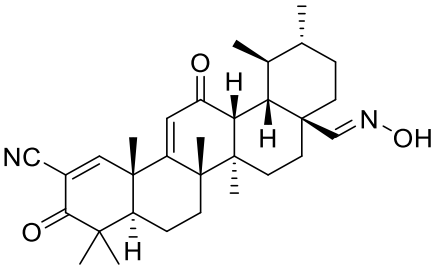
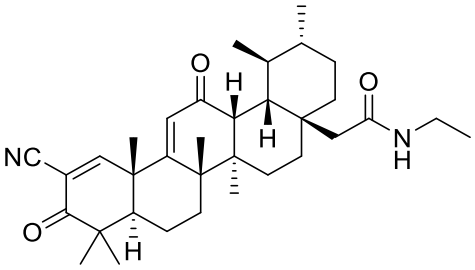
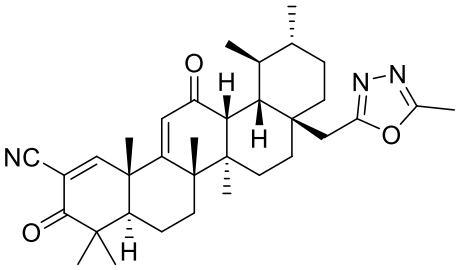
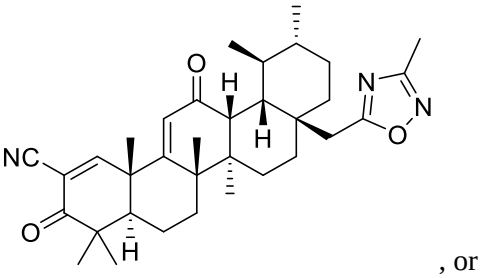
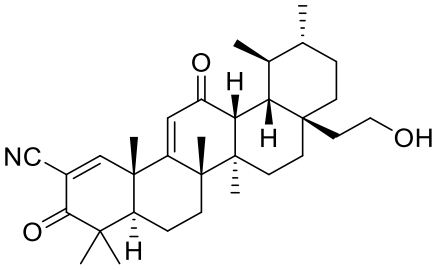
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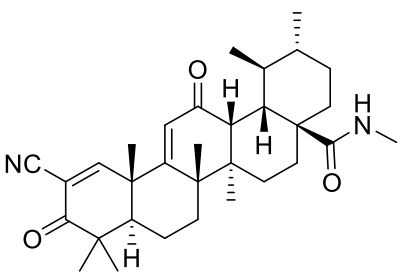












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or a pharmaceutically acceptable salt thereof.

72. A compound of the formula:


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or a pharmaceutically acceptable salt thereof.

73. A pharmaceutical composition comprising:

(A) a compound according to any one of claims 1-72; and

(B) an excipient.

74. The compound or pharmaceutical composition according to any one of claims 1-73 for use in treatment or prevention of a disease or disorder in a patient.

75. Use of a compound or pharmaceutical composition according to any one of claims 1-73 in the manufacture of a medicament for the treatment or prevention of a disease or disorder in a patient.

76. The use of claim 75, wherein the disease or disorder is a condition associated with inflammation and/or oxidative stress.

77. Use of the compound or pharmaceutical composition according to any one of claims 1-73 in the manufacture of a medicament for the inhibition of nitric oxide production in one or more cells of a patient.