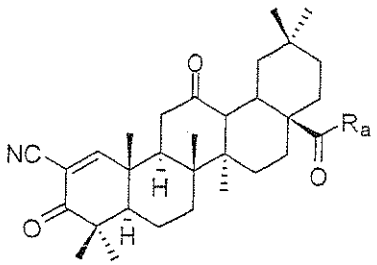
SUMMARY ~~OF THE INVENTION~~

The present disclosure provides new compounds with antioxidant and anti-inflammatory properties, methods for their manufacture, and methods for their use. Compounds covered by the generic or specific formulas below or specifically named are referred to as "compounds of the invention," "compounds of the present disclosure," "the present oleanolic acid derivatives" in the present application.

In a first aspect, the present invention refers to a compound of the formula:



,

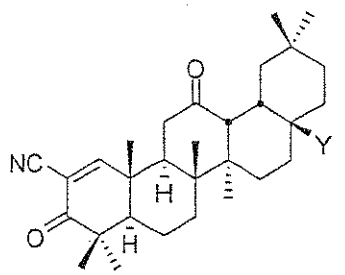
wherein R_a is:

hydrogen, hydroxy, halo or amino; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heteroaralkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $alkynyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $heteroaralkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $alkoxyamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $alkynylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $heteroaralkylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

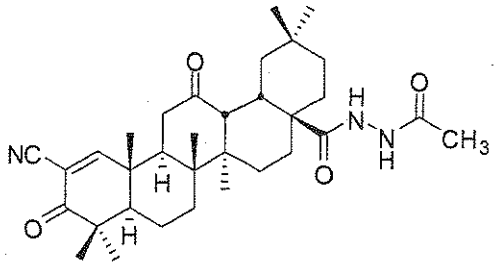
In a second aspect, the present invention refers to a compound of the formula:



,

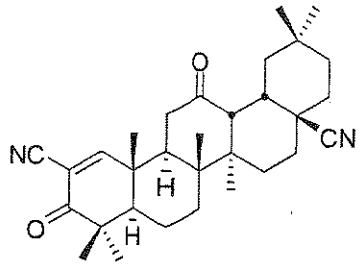
wherein Y is $heteroaryl_{(C\leq 8)}$ or a substituted $heteroaryl_{(C\leq 8)}$; or a pharmaceutically acceptable salt or a tautomer thereof.

In a third aspect, the present invention refers to a compound of the formula:



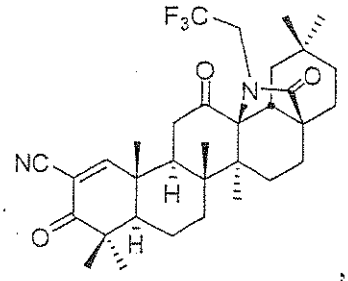
or a pharmaceutically acceptable salt or tautomer thereof.

In a fourth aspect, the present invention refers to a compound of the formula:



or a pharmaceutically acceptable salt or tautomer thereof.

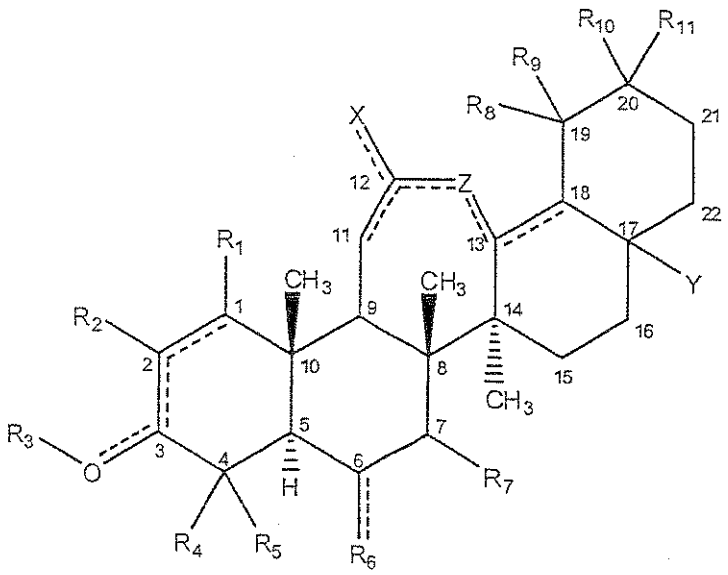
In a fifth aspect, the present invention refers to a compound of the formula:



or a pharmaceutically acceptable salt or tautomer thereof.

In a sixth aspect, the present invention refers to a pharmaceutical composition comprising as an active ingredient a compound as defined above and a pharmaceutically acceptable carrier.

In some ~~aspects~~examples, the disclosure provides compounds of the formula:



(I),

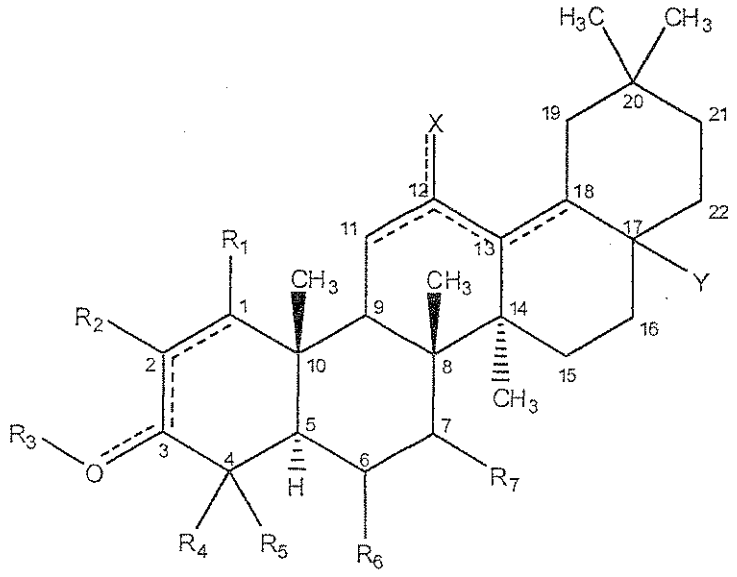
wherein:

Y is cyano, heteroaryl$_{(C\leq12)}$, substituted heteroaryl$_{(C\leq12)}$, or $-C(O)R_a$, further wherein R_a is:

hydrogen, hydroxy, halo, amino, hydroxyamino, azido, silyl or mercapto;

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, alkenyloxy$_{(C\leq12)}$, alkynyloxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkoxyamino$_{(C\leq12)}$, alkenylamino$_{(C\leq12)}$, alkynylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, heteroaralkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, alkyl-

In some ~~embodiments~~examples, the compound is further defined as:



(II),

wherein:

Y is cyano, or $-C(O)R_a$, further wherein:

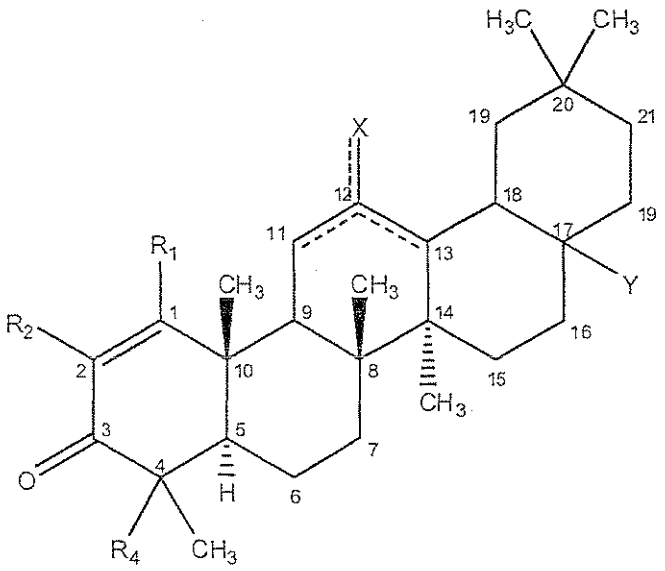
R_a is:

hydrogen, hydroxy, halo, amino, hydroxyamino, azido or mercapto; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylthio_{(C\leq12)}$, $alkenylthio_{(C\leq12)}$, $alkynylthio_{(C\leq12)}$, $arylthio_{(C\leq12)}$, $aralkylthio_{(C\leq12)}$, $heteroarylthio_{(C\leq12)}$, $heteroaralkylthio_{(C\leq12)}$, $acylthio_{(C\leq12)}$, $alkylammonium_{(C\leq12)}$, $alkylsulfonium_{(C\leq12)}$, $alkylsilyl_{(C\leq12)}$, or a substituted version of any of these groups;

X is OR_b, NR_bR_c, or SR_b, wherein R_b and R_c are each independently:

hydrogen or hydroxy;

In some ~~embodiments~~examples, the compound is further defined as:



(III),

wherein:

Y is cyano or $-C(O)R_a$, further wherein:

R_a is:

hydrogen, hydroxy, halo, amino, azido, mercapto or silyl; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

X is OR_b, NR_bR_c, or SR_b, wherein R_b and R_c are each independently:

hydrogen or hydroxy;

$alkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, or a substituted version of any of these groups; or

a substituent convertible *in vivo* to hydrogen;

provided that R_b is absent when the atom to which it is bound is part of a double bond, further provided that when R_b is absent the atom to which it is bound is part of a double bond;

R_1 is:

hydrogen, cyano, hydroxy, halo or amino; or

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

R_2 is:

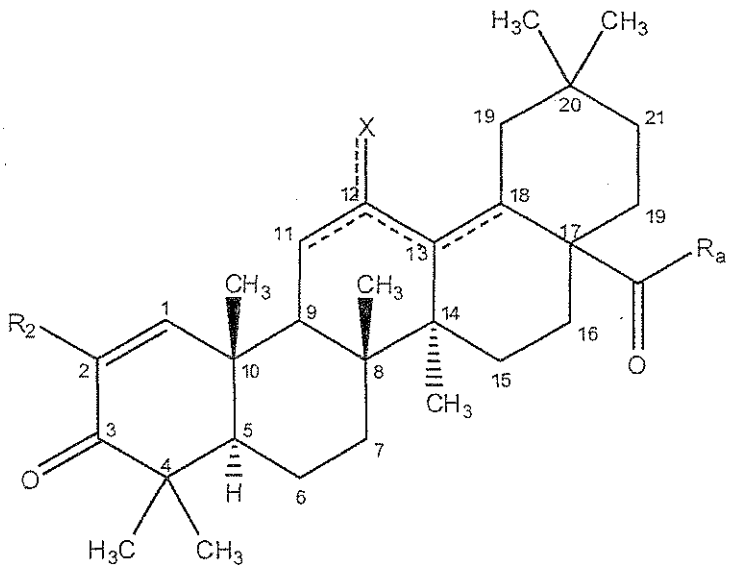
cyano, hydroxy, halo or amino; or

$fluoroalkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_4 is $alkyl_{(C\leq 8)}$ or substituted $alkyl_{(C\leq 8)}$;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some ~~embodiments~~examples, the compound is further defined as:



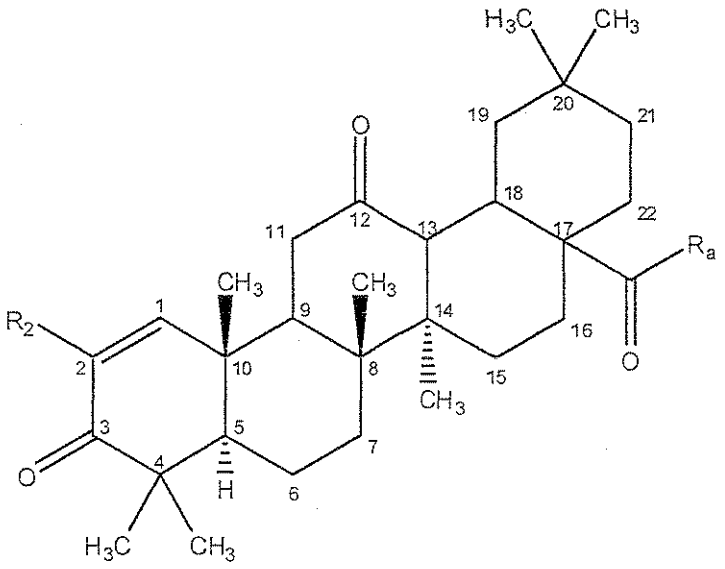
(IV),

wherein:

R_a is:

hydrogen, hydroxy, halo, or amino; or

In some ~~embodiments~~examples, the compound is further defined as:



(V),

wherein:

R_a is:

hydrogen, hydroxy, halo, or amino; or

$alkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heteroaralkyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $alkenyloxy_{(C\leq8)}$, $alkynyloxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $aralkoxy_{(C\leq8)}$, $heteroaryloxy_{(C\leq8)}$, $heteroaralkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $alkoxyamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkenylamino_{(C\leq8)}$, $alkynylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $aralkylamino_{(C\leq8)}$, $heteroarylamino_{(C\leq8)}$, $heteroaralkylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, or a substituted version of any of these groups; and

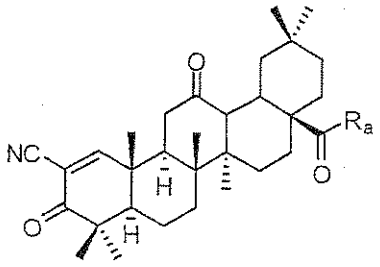
R_2 is:

cyano or fluoro; or

$fluoroalkyl_{(C\leq5)}$, $alkenyl_{(C\leq5)}$, $alkynyl_{(C\leq5)}$, $heteroaryl_{(C\leq5)}$, $acyl_{(C\leq5)}$, $acyloxy_{(C\leq5)}$, $amido_{(C\leq5)}$, or a substituted version of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some ~~embodiments~~examples, the compound is further defined as:



(VI),

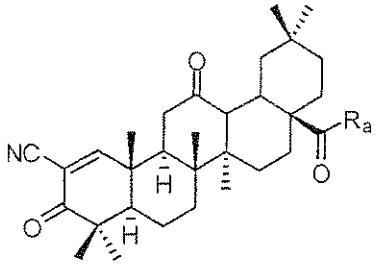
wherein R_a is:

hydrogen, hydroxy, halo or amino; or

$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heteroaralkyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $alkynyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $heteroaralkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $alkoxyamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $alkynylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $heteroaralkylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, or a substituted version of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

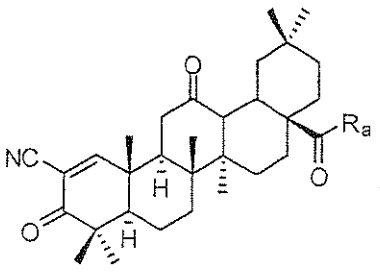
In some ~~embodiments~~examples, the compound is further defined as:



(VII),

wherein R_a is $alkoxy_{(C1-4)}$, $alkylamino_{(C1-4)}$, $alkoxyamino_{(C1-4)}$, $dialkylamino_{(C2-4)}$, or a substituted version of any of these groups; or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

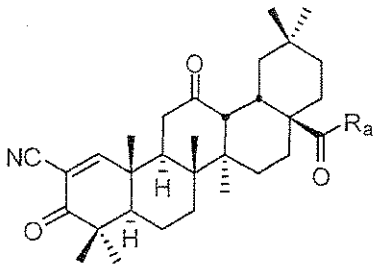
In some ~~embodiments~~examples, the compound is further defined as:



(VIII),

wherein R_a is $alkyl_{(C1-4)}$ or $aralkoxy_{(C7-8)}$ or a substituted version of either of these groups; or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

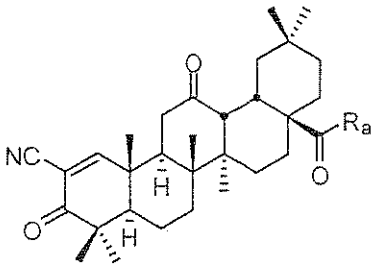
In some ~~embodiments~~examples, the compound is further defined as:



(IX),

wherein R_a is hydrogen, hydroxy, amino, dimethylamino, methyl, methoxy, methoxyamino, benzyloxy, or 2,2,2-trifluoroethylamino; or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

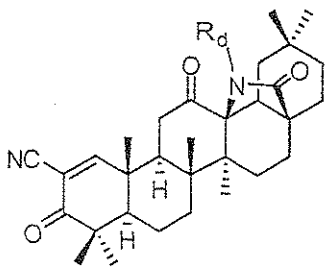
In some ~~embodiments~~examples, the compound is further defined as:



(X),

wherein R_a is hydrogen, hydroxy, amino, methoxy, or 2,2,2-trifluoroethylamino; or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

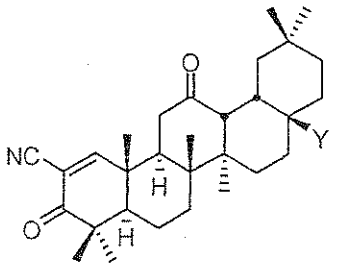
In some ~~embodiments~~examples, the compound is further defined as:



(XI),

wherein R_d is $alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heteroaralkyl_{(C\leq 8)}$, or a substituted version of any of these groups; or pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

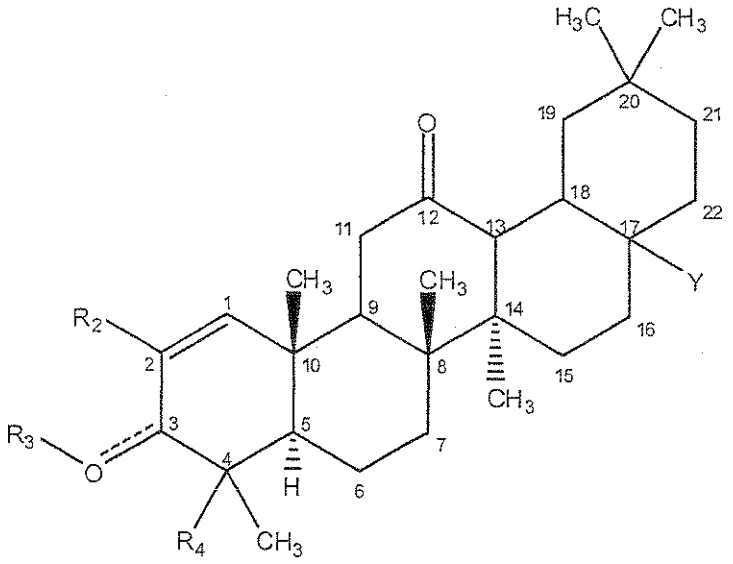
In some ~~embodiments~~examples, the compound is further defined as:



(XII),

wherein Y is $heteroaryl_{(C\leq 8)}$ or a substituted $heteroaryl_{(C\leq 8)}$; or a pharmaceutically acceptable salts, hydrates, solvates, tautomers, or optical isomers thereof.

In some ~~embodiments~~examples, the compound is further defined as:

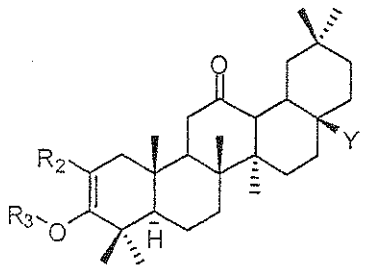


(XIII),

wherein:

wherein Y is cyano or $-C(O)R_a$, further wherein:

In some ~~embodiments~~examples, the compound is further defined as:



(XIV),

wherein:

Y is cyano or $-C(O)R_a$, wherein

R_a is:

hydrogen, hydroxy, halo, amino, hydroxyamino, azido or mercapto; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

R_2 is:

cyano, hydroxy, halo or amino; or

$fluoroalkyl_{(C\leq8)}$, $alkenyl_{(C\leq8)}$, $alkynyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $aryloxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $arylamino_{(C\leq8)}$, $amido_{(C\leq8)}$, or a substituted version of any of these groups; and

R_3 is:

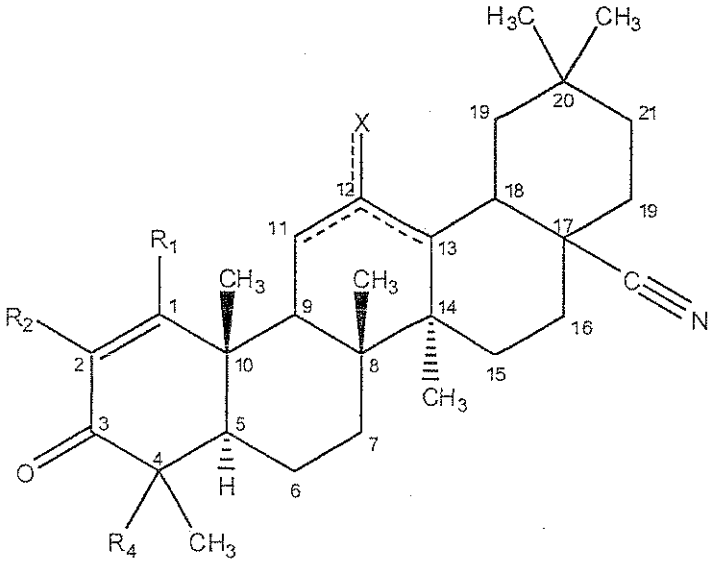
hydrogen;

$alkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, or a substituted version of any of these groups; or

a substituent convertible *in vivo* to hydrogen;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some ~~embodiments~~examples, the compound is further defined as:



(XV),

wherein:

X is OR_b, NR_bR_c, or SR_b, wherein R_b and R_c are each independently:

hydrogen;

$alkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

a substituent convertible *in vivo* to hydrogen;

provided that R_b is absent when the atom to which it is bound is part of a double bond, further provided that when R_b is absent the atom to which it is bound is part of a double bond;

R_1 is:

hydrogen, cyano, hydroxy, halo or amino; or

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

R_2 is:

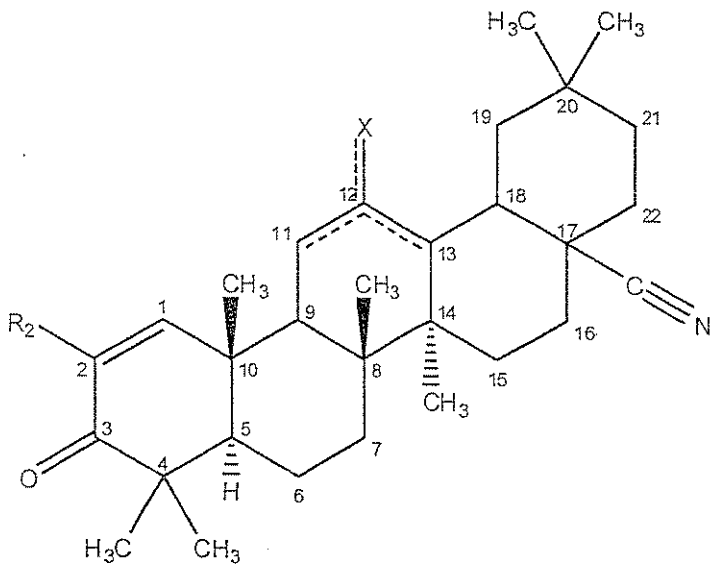
cyano, hydroxy, halo or amino; or

$fluoroalkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_4 is $alkyl_{(C\leq 8)}$ or substituted $alkyl_{(C\leq 8)}$;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some ~~embodiments~~examples, the compound is further defined as:



(XVI),

wherein:

X is OR_b or NR_bR_c, wherein R_b and R_c are each independently:

hydrogen;

$alkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

a substituent convertible *in vivo* to hydrogen;

provided that R_b is absent when the atom to which it is bound is part of a double bond, further provided that when R_b is absent the atom to which it is bound is part of a double bond; and

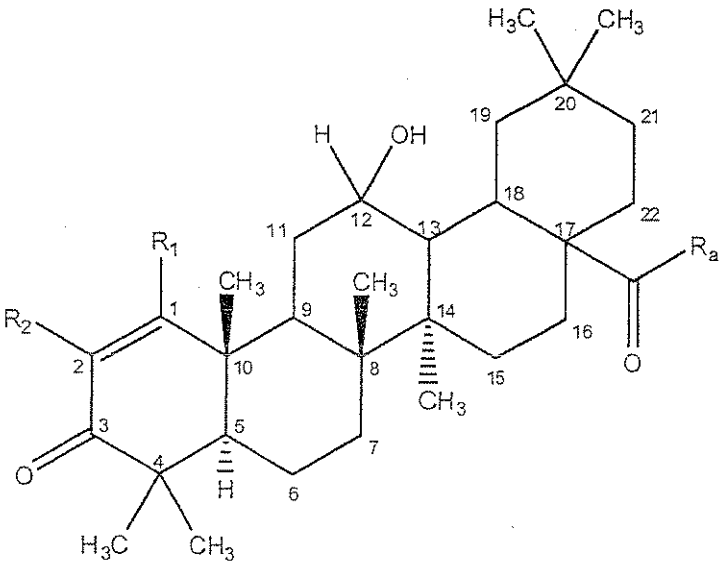
R_2 is:

cyano, hydroxy, halo or amino; or

$fluoroalkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, or a substituted version of any of these groups;

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some ~~embodiments~~examples, the compound is further defined as:



(XVII),

wherein:

R_a is:

hydrogen, hydroxy, halo, amino, azido, mercapto or silyl; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

R_1 is:

hydrogen, cyano, hydroxy, halo or amino; or

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

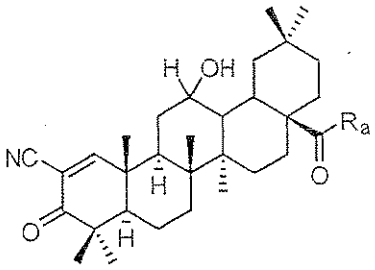
R_2 is:

cyano, hydroxy, halo or amino; or

fluoroalkyl$_{(C\leq8)}$, alkenyl$_{(C\leq8)}$, alkynyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, aryloxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, arylamino$_{(C\leq8)}$, amido$_{(C\leq8)}$, or a substituted version of any of these groups; and

or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some ~~embodiments~~examples, the compound is further defined as:



(XVIII),

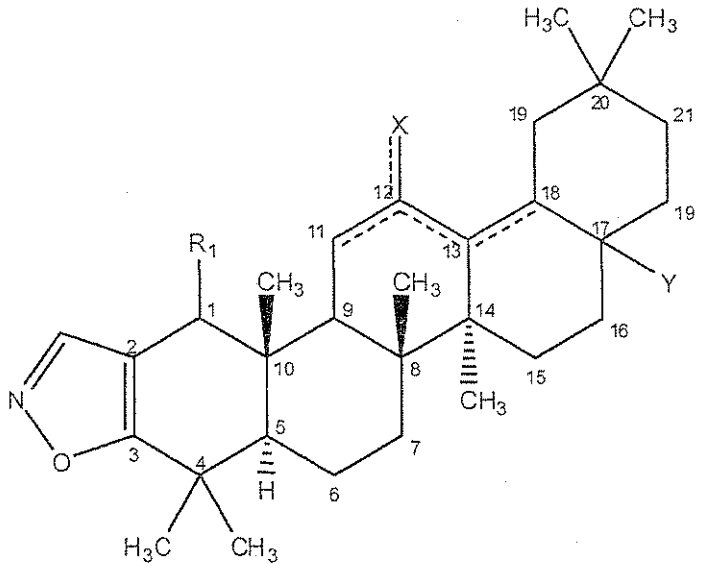
wherein R_a is:

hydrogen, hydroxy, halo or amino; or

alkyl$_{(C\leq6)}$, aryl$_{(C\leq8)}$, aralkyl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, alkoxy$_{(C\leq6)}$, aryloxy$_{(C\leq8)}$, aralkoxy$_{(C\leq8)}$, alkylamino$_{(C\leq6)}$, alkoxyamino$_{(C\leq6)}$, alkoxyamino$_{(C\leq6)}$, dialkylamino$_{(C\leq6)}$, arylamino$_{(C\leq8)}$, aralkylamino$_{(C\leq8)}$, heteroarylamino$_{(C\leq6)}$, heteroarylamino$_{(C\leq8)}$, amido$_{(C\leq6)}$, or a substituted version of any of these groups;

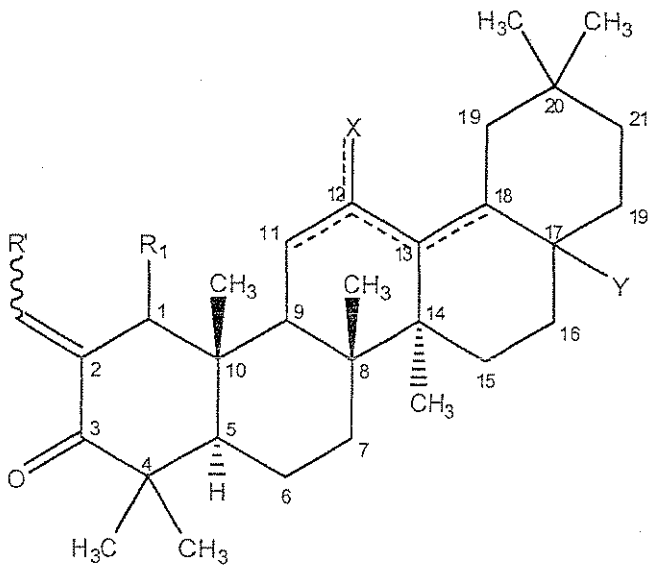
or pharmaceutically acceptable salts, esters, hydrates, solvates, tautomers, prodrugs, or optical isomers thereof.

In some ~~aspects~~examples, the disclosure provides compounds of the formula:



(XIX),

In some ~~aspects~~examples, the disclosure provides compounds of the formula:



(XX),

wherein:

Y is cyano or $-C(O)R_a$, wherein

R_a is:

hydrogen, hydroxy, halo, amino, hydroxyamino, azido or mercapto; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $alkenyloxy_{(C\leq12)}$, $alkynyloxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $heteroaralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkoxyamino_{(C\leq12)}$, $alkenylamino_{(C\leq12)}$, $alkynylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $heteroaralkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, $alkylthio_{(C\leq12)}$, $alkenylthio_{(C\leq12)}$, $alkynylthio_{(C\leq12)}$, $arylthio_{(C\leq12)}$, $aralkylthio_{(C\leq12)}$, $heteroarylthio_{(C\leq12)}$, $heteroaralkylthio_{(C\leq12)}$, $acylthio_{(C\leq12)}$, $alkylammonium_{(C\leq12)}$, $alkylsulfonium_{(C\leq12)}$, $alkylsilyl_{(C\leq12)}$, or a substituted version of any of these groups;

X is OR_b, NR_bR_c, or SR_b, wherein R_b and R_c are each independently:

hydrogen;

$alkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $aralkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, or a substituted version of any of these groups; or

provided that R_b is absent when the atom to which it is bound is part of a double bond, further provided that when R_b is absent the atom to which it is bound is part of a double bond; and

R_1 is:

hydrogen, cyano, hydroxy, halo or amino; or

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

R′ is hydroxy, $alkoxy_{(C\leq12)}$, substituted $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, substituted $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, substituted $aralkoxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, or substituted $acyloxy_{(C\leq12)}$;

or salts, esters, hydrates, solvates, tautomers, or optical isomers thereof.

In a variation of each of the above ~~embodiments~~examples containing a Z group, Z can be a single bond, –O–, or –NH–. In a variation of each of the above ~~embodiments~~examples containing an X group, X can be OR_b. In some variations, R_b is absent. In other variations, R_b is hydrogen. In other variations, X can be NR_b. In some variations, R_b can be hydroxy. In a variation of each of the above ~~embodiments~~examples containing a Y group, Y can be cyano or $-C(O)R_a$. In some variations, R_a can be hydroxy. In some variations, R_a can be $alkoxy_{(C\leq6)}$, $aryloxy_{(C\leq8)}$, $aralkyloxy_{(C\leq8)}$, or a substituted version of any of these groups. In some of these variations, R_a can be $alkoxy_{(C2\text{-}6)}$. In some of these variations, R_a can be $alkoxy_{(C1\text{-}5)}$ or substituted $alkoxy_{(C1\text{-}5)}$. In some of these variations, R_a can be $alkoxy_{(C2\text{-}4)}$ or substituted $alkoxy_{(C2\text{-}4)}$. In some of these variations, R_a can be $alkoxy_{(C1\text{-}4)}$ or substituted $alkoxy_{(C1\text{-}4)}$. In some of these variations, R_a can be $alkoxy_{(C1\text{-}2)}$ or substituted $alkoxy_{(C1\text{-}2)}$. For example, R_a can be methoxy. In some variations, R_a can be amino. In some variations, R_a can be $alkylamino_{(C1\text{-}6)}$, $alkoxyamino_{(C1\text{-}6)}$, $arylamino_{(C1\text{-}8)}$, $aralkylamino_{(C1\text{-}8)}$, $dialkylamino_{(C2\text{-}8)}$, or a substituted version of any of these groups. In some of these variations, R_a can be $alkylamino_{(C2\text{-}6)}$ or substituted $alkylamino_{(C2\text{-}6)}$. In some of these variations, R_a can be $alkylamino_{(C3\text{-}6)}$. In some variations, R_a can be $alkylamino_{(C1\text{-}5)}$, $dialkylamino_{(C2\text{-}6)}$, or substituted version of either of these groups. In some variations, R_a can be $alkylamino_{(C2\text{-}4)}$, $dialkylamino_{(C2\text{-}5)}$, or substituted version of either of these groups. In some variations, R_a can be $alkylamino_{(C1\text{-}4)}$ or substituted $alkylamino_{(C1\text{-}4)}$. In some variations, R_a can be $alkylamino_{(C1\text{-}3)}$. In some of these variations,

R_a can be methylamino or ethylamino. In some of these variations, R_a can be substituted alkylamino$_{(C1-3)}$. For example, R_a can be 2,2,2-trifluoroethylamino. In some of these variations, R_a can be alkyl$_{(C1-5)}$, aryl$_{(C\leq8)}$, aralkyl$_{(C\leq8)}$, heteroaralkyl$_{(C\leq8)}$, or a substituted version of any of these groups. In some of these variations, R_a can be heteroaryl$_{(C1-8)}$ or substituted heteroaryl$_{(C1-8)}$. For example, wherein R_a can be imidazolyl. In some of these variations, R_a can be –H.

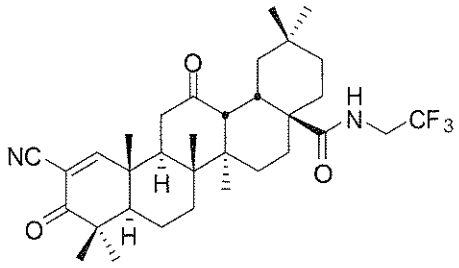
In a variation of each of the above ~~embodiments~~examples containing an R_1 group, R_1 can be –H, –OH or –F. For example, R_1 can be –H. In a variation of each of the above ~~embodiments~~examples containing an R_2 group, R_2 can be –CN. In some variations, R_2 can be a substituted acyl$_{(C1-3)}$, such as $-C(=O)NHS(=O)_2CH_3$. In some variations, R_2 is fluoroalkyl$_{(C\leq8)}$. For example, R_2 can be $-CF_3$. In other variations, R_2 is not fluoroalkyl$_{(C\leq8)}$.

In a variation of each of the above ~~embodiments~~examples containing an R_3 group, R_3 can be hydrogen or acetyl. In another variation, R_3 can be absent. In a variation of each of the above ~~embodiments~~examples containing an R_4 group, R_4 can be methyl or hydroxymethyl. In a variation of each of the above ~~embodiments~~examples containing an R_6, R_7, R_8, or R_9 group, R_6, R_7, R_8, or R_9 can independently be hydrogen. In a variation of each of the above ~~embodiments~~examples containing an R_{10} or R_{11} group, R_{10} or R_{11} can independently be methyl. In a variation of each of the above ~~embodiments~~examples containing an R′ group, R′ can be acetyloxy or hydroxy.

In a variation of each of the above ~~embodiments~~examples containing an R_d group, R_d can be alkyl$_{(C1-5)}$, aryl$_{(C\leq8)}$, aralkyl$_{(C\leq8)}$, heteroaralkyl$_{(C\leq8)}$, or a substituted version of any of these groups. In some variations, R_d can be alkyl$_{(C1-4)}$ or a substituted version thereof. In some variations, R_d can be alkyl$_{(C1-3)}$ or a substituted version thereof. In some variations, R_d can be alkyl$_{(C1-2)}$ or a substituted version thereof.

Non-limiting examples of compounds provided by this ~~invention~~disclosure include the compounds according to the formulas shown below, as well as or pharmaceutically acceptable salts thereof. In certain ~~embodiments~~examples, these compounds are substantially free from other optical isomers thereof.

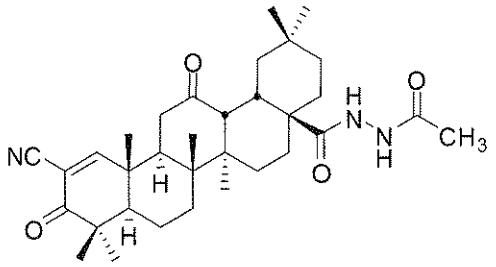
15. The compound of claim 1, further defined as:



,

or a pharmaceutically acceptable salt or a tautomer thereof.

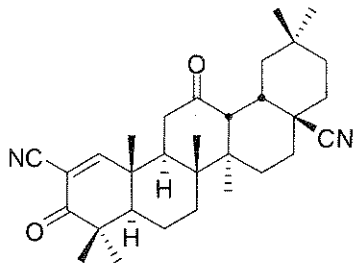
16. ~~The compound of claim 1, further defined as~~A compound of the formula:



,

or a pharmaceutically acceptable salt or tautomer thereof.

17. A compound of the formula:



,

or a pharmaceutically acceptable salt or tautomer thereof.