leading to chronic, "smoldering" inflammation. This effect may be responsible for the increased incidence of cardiovascular disease in patients using selective COX-2 inhibitors for long periods of time. Corticosteroids, another important class of anti-inflammatory drugs, have many undesirable side effects and frequently are not suitable for chronic use. Newer protein-based drugs, such as anti-TNF monoclonal antibodies, have proven to be effective for the treatment of certain autoimmune diseases such as rheumatoid arthritis. However, these compounds must be administered by injection, are not effective in all patients, and may have severe side effects. In many severe forms of inflammation (*e.g.*, sepsis, acute pancreatitis), existing drugs are ineffective. In addition, currently available drugs do not have significant antioxidant properties, and are not effective in reducing oxidative stress associated with excessive production of reactive oxygen species and related molecules such as peroxynitrite. Accordingly, there is a pressing need for improved therapeutics with antioxidant and anti-inflammatory properties.

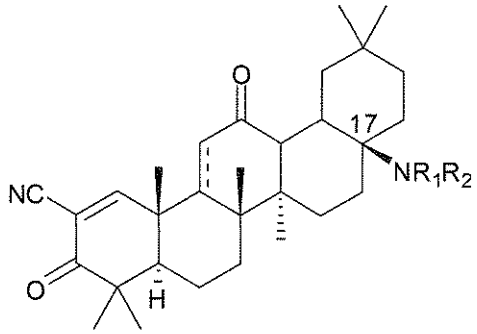
A series of synthetic triterpenoid analogs of oleanolic acid have been shown to be inhibitors of cellular inflammatory processes, such as the induction by IFN-γ of inducible nitric oxide synthase (iNOS) and of COX-2 in mouse macrophages. See Honda *et al.* (2000a); Honda *et al.* (2000b), and Honda *et al.* (2002), which are all incorporated herein by reference. For example, one of these, 2-cyano-3,12-dioxooleane-1,9(11)-dien-28-oic acid methyl ester (CDDO-Me), is currently in clinical trials for a variety of disorders related to inflammation, including cancer and diabetic nephropathy. The pharmacology of these molecules is complex, as they have been shown to affect the function of multiple protein targets and thereby modulate the function of several important cellular signaling pathways related to oxidative stress, cell cycle control, and inflammation (*e.g.*, Dinkova-Kostova *et al.*, 2005; Ahmad *et al.*, 2006; Ahmad *et al.*, 2008; Liby *et al.*, 2007). Given that the biological activity profiles of the known oleanolic acid derivatives vary, and in view of the wide variety of diseases that may be treated with compounds having potent antioxidant and anti-inflammatory effects, it is desirable to synthesize new candidates for the treatment or prevention of disease.

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," or "oleanolic acid derivatives" in the present application.

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



wherein:

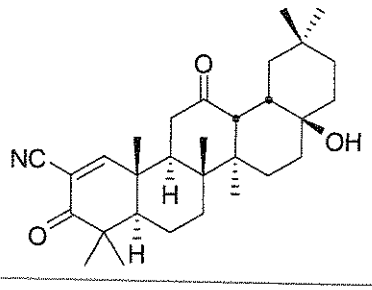
R_1 and R_2 are independently:

hydrogen; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, alkylsulphonyl, $alkenylsulphonyl_{(C\leq12)}$, $alkynylsulphonyl_{(C\leq12)}$, $arylsulphonyl_{(C\leq12)}$, $aralkylsulphonyl_{(C\leq12)}$, $heteroarylsulphonyl_{(C\leq12)}$, $heteroaralkylsulphonyl_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

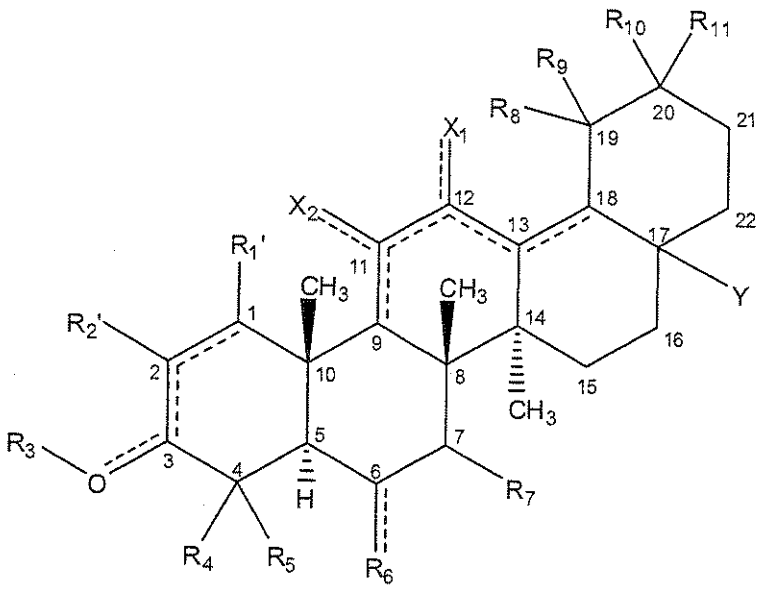
In a second aspect, the present invention refers to a compound of the formula:



or a pharmaceutically acceptable salt or tautomer thereof.

In a third 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 exampleaspeets, the disclosure provides compounds of the formula:



(I)

wherein:

X_1 and X_2 are independently:

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

hydrogen or hydroxy;

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

a substituent convertible *in vivo* to hydrogen;

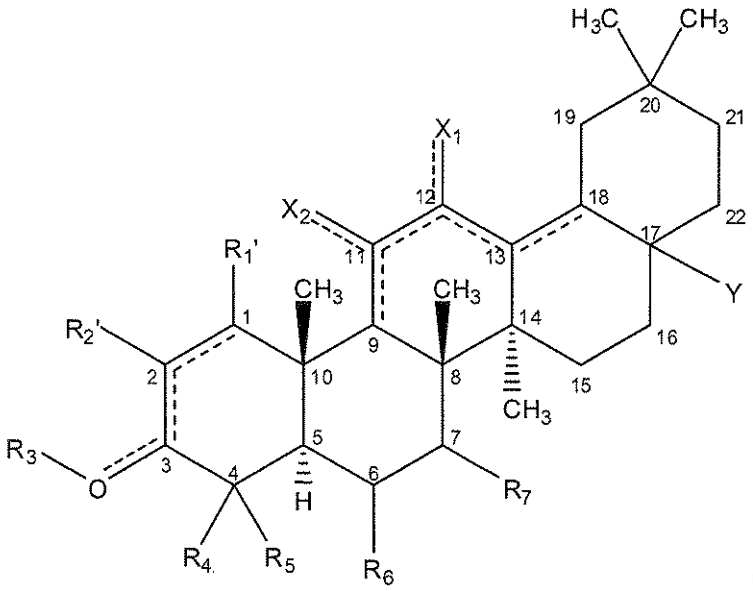
provided that R_b is absent when the atom to which it is bound is part of a double bond, further provided that when R_b is absent the atom to which it is bound is part of a double bond;

Y is hydroxy, $alkoxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, substituted $alkoxy_{(C\leq 8)}$, substituted $alkoxy_{(C\leq 8)}$, substituted $aryloxy_{(C\leq 8)}$, substituted $acyloxy_{(C\leq 8)}$, or NR_1R_2, wherein R_1 and R_2 are independently:

hydrogen or hydroxy; or

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$,

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



(II)

wherein:

X_1 and X_2 are independently:

hydrogen, 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;

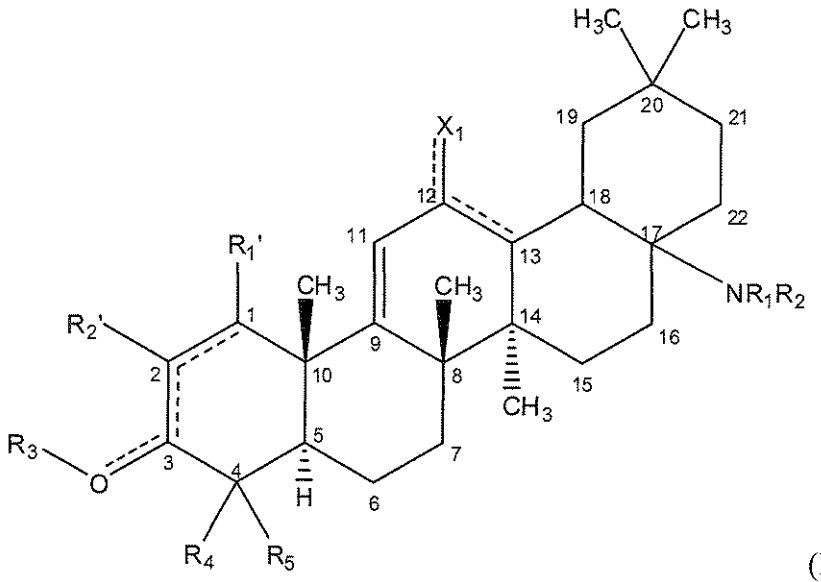
Y is hydroxy or NR_1R_2, wherein:

R_1 and R_2 are independently:

hydrogen or hydroxy; or

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $thioacyl_{(C\leq 12)}$, $alkylsulfonyl_{(C\leq 12)}$, $alkenylsulfonyl_{(C\leq 12)}$, $alkynylsulfonyl_{(C\leq 12)}$, $arylsulfonyl_{(C\leq 12)}$, $aralkylsulfonyl_{(C\leq 12)}$, $heteroarylsulfonyl_{(C\leq 12)}$,

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



(III)

wherein:

X_1 is:

hydrogen, 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;

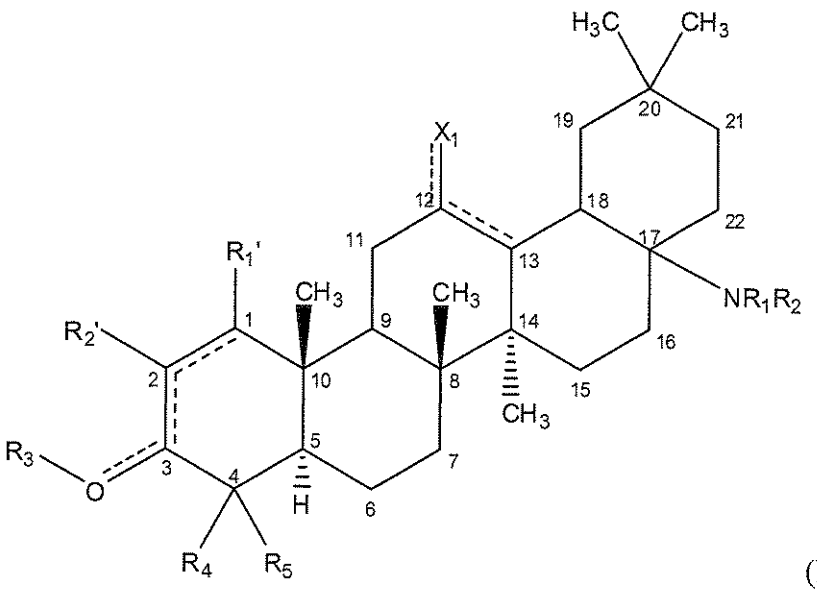
R_1 and R_2 are independently:

hydrogen or hydroxy; or

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $thioacyl_{(C\leq 12)}$, $alkylsulfonyl_{(C\leq 12)}$, $alkenylsulfonyl_{(C\leq 12)}$, $alkynylsulfonyl_{(C\leq 12)}$, $arylsulfonyl_{(C\leq 12)}$, $aralkylsulfonyl_{(C\leq 12)}$, $heteroarylsulfonyl_{(C\leq 12)}$, or $heteroaralkylsulfonyl_{(C\leq 12)}$, or a substituted version of any of these groups;

R_1' is:

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



(IV)

wherein:

X_1 is:

hydrogen, 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;

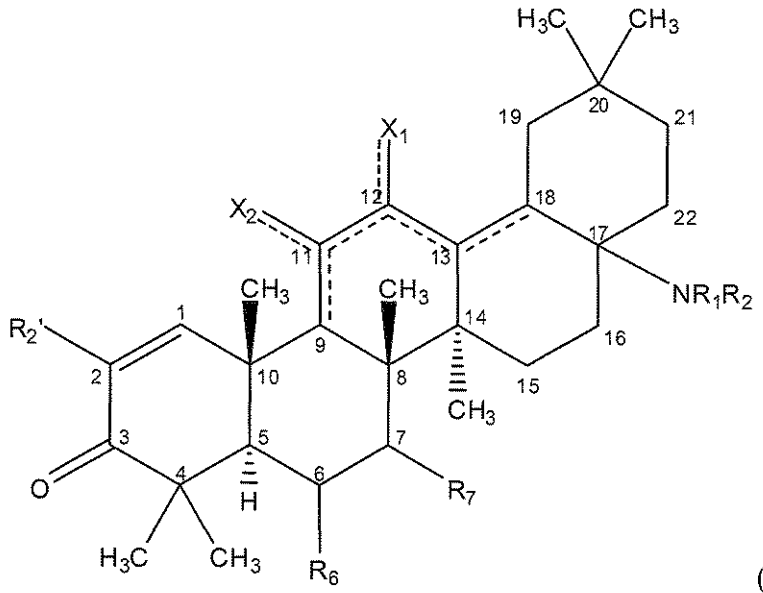
R_1 and R_2 are independently:

hydrogen or hydroxy; or

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $thioacyl_{(C\leq 12)}$, $alkylsulfonyl_{(C\leq 12)}$, $alkenylsulfonyl_{(C\leq 12)}$, $alkynylsulfonyl_{(C\leq 12)}$, $arylsulfonyl_{(C\leq 12)}$, $aralkylsulfonyl_{(C\leq 12)}$, $heteroarylsulfonyl_{(C\leq 12)}$, or $heteroaralkylsulfonyl_{(C\leq 12)}$, or a substituted version of any of these groups;

R_1' is:

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



(V)

wherein:

X_1 and X_2 are independently:

hydrogen, 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 and R_2 are independently:

hydrogen or hydroxy; or

$alkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $alkenyloxy_{(C\leq 12)}$, $alkynyloxy_{(C\leq 12)}$, $aryloxy_{(C\leq 12)}$, $aralkoxy_{(C\leq 12)}$, $heteroaryloxy_{(C\leq 12)}$, $heteroaralkoxy_{(C\leq 12)}$, $thioacyl_{(C\leq 12)}$, $alkylsulfonyl_{(C\leq 12)}$, $alkenylsulfonyl_{(C\leq 12)}$, $alkynylsulfonyl_{(C\leq 12)}$, $arylsulfonyl_{(C\leq 12)}$, $aralkylsulfonyl_{(C\leq 12)}$, $heteroarylsulfonyl_{(C\leq 12)}$, or $heteroaralkylsulfonyl_{(C\leq 12)}$, or a substituted version of any of these groups;

R_2' is:

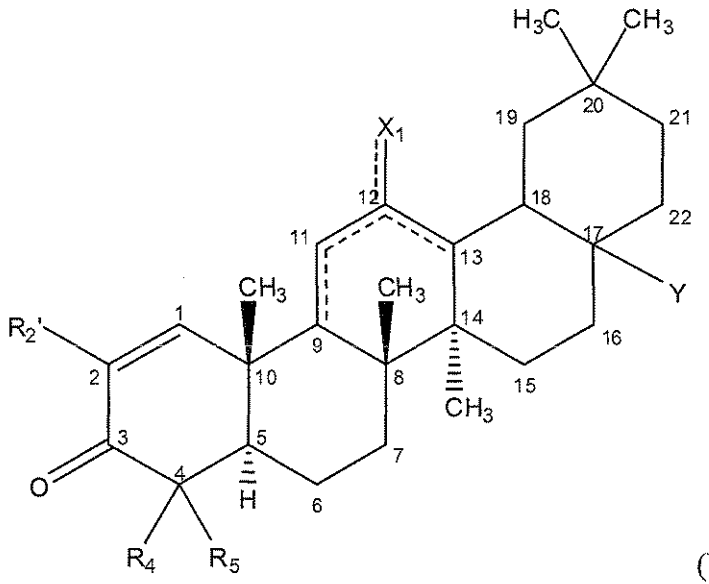
cyano, hydroxy, halo or amino; or

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;

R_6 and R_7 are each independently hydrogen or hydroxy;

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

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



(VI)

wherein:

X_1 is:

hydrogen, 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;

Y is hydroxy or NR_1R_2, wherein:

R_1 and R_2 are independently:

hydrogen or hydroxy; or

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, alkenyloxy$_{(C\leq12)}$, alkynyloxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, heteroaralkoxy$_{(C\leq12)}$, thioacyl$_{(C\leq12)}$, alkylsulfonyl$_{(C\leq12)}$, alkenylsulfonyl$_{(C\leq12)}$, alkynylsulfonyl$_{(C\leq12)}$, arylsulfonyl$_{(C\leq12)}$, aralkylsulfonyl$_{(C\leq12)}$, heteroarylsulfonyl$_{(C\leq12)}$, or heteroaralkylsulfonyl$_{(C\leq12)}$, or a substituted version of any of these groups;

R_2' is:

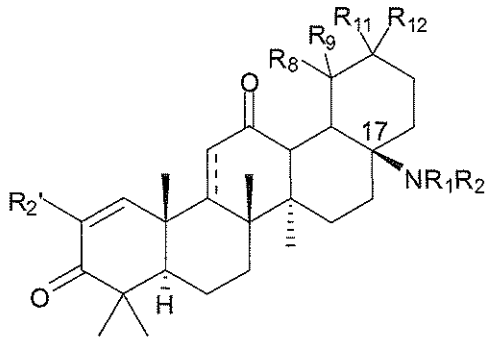
cyano, hydroxy, halo or amino; or

fluoroalkyl$_{(C\leq8)}$, 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_4 and R_5 are each independently alkyl$_{(C\leq8)}$ or substituted alkyl$_{(C\leq8)}$;

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

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



(VII)

wherein:

R_2' is:

cyano, hydroxy, halo or amino; or

fluoroalkyl$_{(C\leq 8)}$, 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_1 and R_2 are independently:

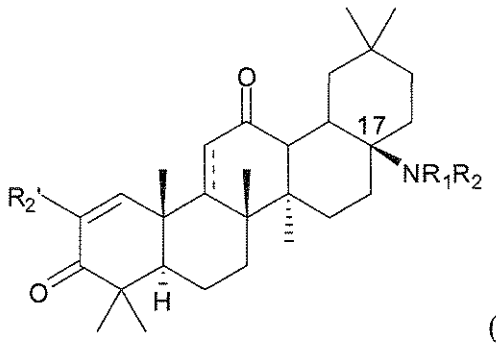
hydrogen; or

alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, alkylsulphonyl, alkenylsulphonyl$_{(C\leq 12)}$, alkynylsulphonyl$_{(C\leq 12)}$, arylsulphonyl$_{(C\leq 12)}$, aralkylsulphonyl$_{(C\leq 12)}$, heteroarylsulphonyl$_{(C\leq 12)}$, heteroaralkylsulphonyl$_{(C\leq 12)}$, or a substituted version of any of these groups; and

R_8, R_9, R_{10} and R_{11} are each independently hydrogen, hydroxy, alkyl$_{(C\leq 6)}$, substituted alkyl$_{(C\leq 6)}$, alkoxy$_{(C\leq 6)}$ or substituted alkoxy$_{(C\leq 6)}$;

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

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



(VIII)

wherein:

R_2' is:

cyano, hydroxy, halo or amino; or

fluoroalkyl$_{(C\leq 8)}$, 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_1 and R_2 are independently:

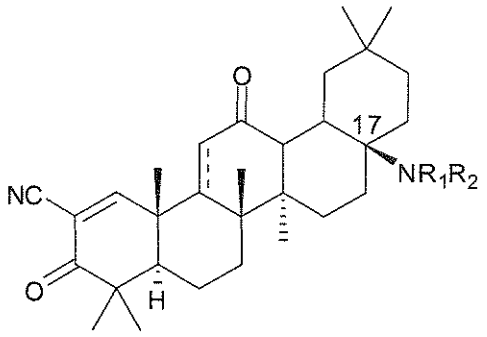
hydrogen; or

alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, heteroaralkyl$_{(C\leq 12)}$, acyl$_{(C\leq 12)}$, alkylsulphonyl, alkenylsulphonyl$_{(C\leq 12)}$,

alkynylsulphonyl$_{(C\leq12)}$, arylsulphonyl$_{(C\leq12)}$, aralkylsulphonyl$_{(C\leq12)}$, heteroarylsulphonyl$_{(C\leq12)}$, heteroaralkylsulphonyl$_{(C\leq12)}$, or a substituted version of any of these groups;

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

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



(IX)

wherein:

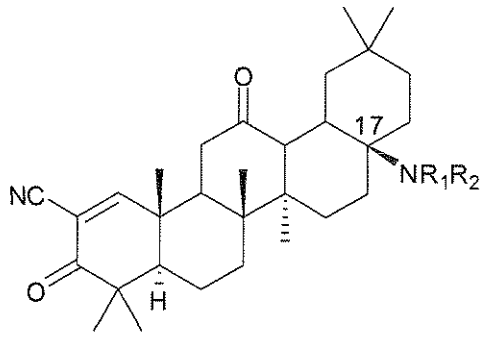
R_1 and R_2 are independently:

hydrogen; or

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkylsulphonyl, alkenylsulphonyl$_{(C\leq12)}$, alkynylsulphonyl$_{(C\leq12)}$, arylsulphonyl$_{(C\leq12)}$, aralkylsulphonyl$_{(C\leq12)}$, heteroarylsulphonyl$_{(C\leq12)}$, heteroaralkylsulphonyl$_{(C\leq12)}$, or a substituted version of any of these groups;

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

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



(X)

wherein:

R_1 and R_2 are independently:

hydrogen; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, alkylsulphonyl, $alkenylsulphonyl_{(C\leq12)}$, $alkynylsulphonyl_{(C\leq12)}$, $arylsulphonyl_{(C\leq12)}$, $aralkylsulphonyl_{(C\leq12)}$, $heteroarylsulphonyl_{(C\leq12)}$, $heteroaralkylsulphonyl_{(C\leq12)}$, or a substituted version of any of these groups;

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

In some variations of one or more of the above ~~embodiments~~examples, X_1 or X_2 is OR_b, wherein R_b is absent. In some variations of one or more of the above ~~embodiments~~examples, X_1 is OR_b and R_b is absent. In some variations of one or more of the above ~~embodiments~~examples, X_2 is hydrogen. In some variations of one or more of the above ~~embodiments~~examples, Y is hydroxy. In some variations of one or more of the above ~~embodiments~~examples, Y is NR_1R_2. In some variations of one or more of the above ~~embodiments~~examples, R_1 or R_2 is hydrogen. In some variations of one or more of the above ~~embodiments~~examples, R_1 and R_2 are each hydrogen. In some variations of one or more of the above ~~embodiments~~examples, R_1 or R_2 comprises a fluoro group. In some variations of one or more of the above ~~embodiments~~examples, R_1 or R_2 comprises a trifluoromethyl group. In some variations of one or more of the above ~~embodiments~~examples, R_1 and R_2 are each independently hydrogen, $alkyl_{(C\leq8)}$, $aryl_{(C\leq10)}$, $aralkyl_{(C\leq10)}$, $heteroaryl_{(C\leq10)}$, $heteroaralkyl_{(C\leq10)}$, or a substituted version of any of these groups. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $alkyl_{(C\leq8)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $alkyl_{(C3\text{-}12)}$ or substituted $alkyl_{(C3\text{-}12)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $alkyl_{(C\leq4)}$ or substituted $alkyl_{(C\leq4)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $alkylsulphonyl_{(C\leq8)}$, $arylsulphonyl_{(C\leq8)}$, $aralkylsulphonyl_{(C\leq8)}$, $heteroaryl$-$sulphonyl_{(C\leq8)}$, $heteroaralkylsulphonyl_{(C\leq8)}$, or a substituted version of any of these groups. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $alkylsulphonyl_{(C\leq8)}$ or substituted $alkylsulphonyl_{(C\leq8)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $alkylsulphonyl_{(C\leq8)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is substituted $alkylsulphonyl_{(C\leq8)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $arylsulphonyl_{(C\leq8)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is $heteroarylsulphonyl_{(C\leq8)}$. In some variations of one or more of the

above ~~embodiments~~examples, R_2 is $acyl_{(C\leq10)}$. In some variations of one or more of the above ~~embodiments~~examples, R_2 is substituted $acyl_{(C\leq10)}$. In some variations of one or more of the above ~~embodiments~~examples, R_1' is hydrogen. In some variations of one or more of the above ~~embodiments~~examples, R_2' is cyano. In some variations of one or more of the above ~~embodiments~~examples, R_2' is $-CF_3$. In some variations of one or more of the above ~~embodiments~~examples, R_3 is absent. In some variations of one or more of the above ~~embodiments~~examples, R_4 and R_5 are the same. In some variations of one or more of the above ~~embodiments~~examples, R_4 and R_5 are each $alkyl_{(C\leq4)}$. In some variations of one or more of the above ~~embodiments~~examples, R_4 and R_5 are each methyl. In some variations of one or more of the above ~~embodiments~~examples, R_6 and R_7 are each hydrogen. In some variations of one or more of the above ~~embodiments~~examples, the bond joining carbon 1 and carbon 2 is a double bond. In some variations of one or more of the above ~~embodiments~~examples, the bond joining carbon 9 and carbon 11 is a double bond. In some variations of one or more of the above ~~embodiments~~examples, the bond joining carbon 9 and carbon 11 is a single bond. In some variations of one or more of the above ~~embodiments~~examples, the bond joining carbon 12 and carbon 13 is a single bond. In some variations of one or more of the above ~~embodiments~~examples, the bond joining carbon 13 and carbon 18 is a single bond.

Examples of specific compounds provided by the present disclosure include:

(4a*R*,6a*R*,6b*R*,8a*S*,12a*S*,12b*R*,14a*R*,14b*R*)-8a-amino-4,4,6a,6b,11,11,14b-heptamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14,14a,14b-icosahydropicene-2-carbonitrile;

N-((4a*S*,6a*R*,6b*R*,8a*R*,12a*R*,12b*R*,14a*R*,14b*S*)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,12b,13,14,14a,14b-icosahydropicen-4a-yl)methanesulfonamide;

methyl-(4a*S*,6a*R*,6b*S*,8a*R*,12a*S*,14a*R*,14b*S*)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicen-4a-ylcarbamate;

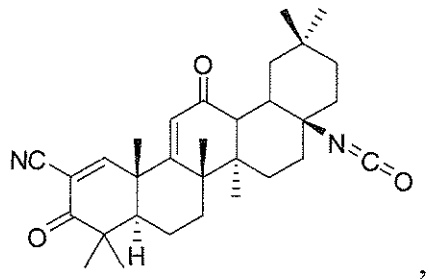
ethyl-(4a*S*,6a*R*,6b*S*,8a*R*,12a*S*,14a*R*,14b*S*)-11-cyano-2,2,6a,6b,9,9,12a-heptamethyl-10,14-dioxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-octadecahydropicen-4a-ylcarbamate;

(4a*R*,6a*S*,6b*R*,8a*S*,12a*S*,12b*R*,14b*S*)-8a-amino-4,4,6a,6b,11,11,14b-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;

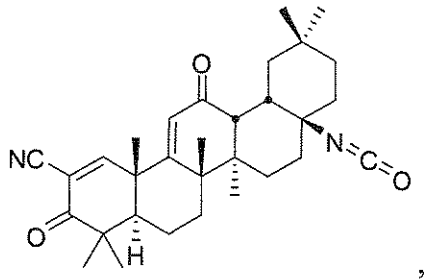
substituted version of any of these groups; or provided that R_3 is absent when the oxygen atom to which it is bound is part of a double bond, further provided that when R_3 is absent the oxygen atom to which it is bound is part of a double bond; R_4 and R_5 are each independently $alkyl_{(C\leq 8)}$ or substituted $alkyl_{(C\leq 8)}$; and R_6 and R_7 are each independently hydrogen or hydroxy; or salts, esters, hydrates, solvates, tautomers, or optical isomers thereof.

In particular ~~embodiments~~examples regarding a compound of formula (IX), R_1' is hydrogen. In certain ~~embodiments~~examples, R_2' is cyano. In certain ~~embodiments~~examples, wherein R_3 is absent. In certain ~~embodiments~~examples, wherein X_2 is hydrogen. In certain ~~embodiments~~examples, wherein the bond joining carbon 1 and carbon 2 is a double bond. In certain ~~embodiments~~examples, wherein the bond joining carbon 9 and carbon 11 is a double bond.

In particular ~~embodiments~~examples, the compound of formula (XI) is further defined as:

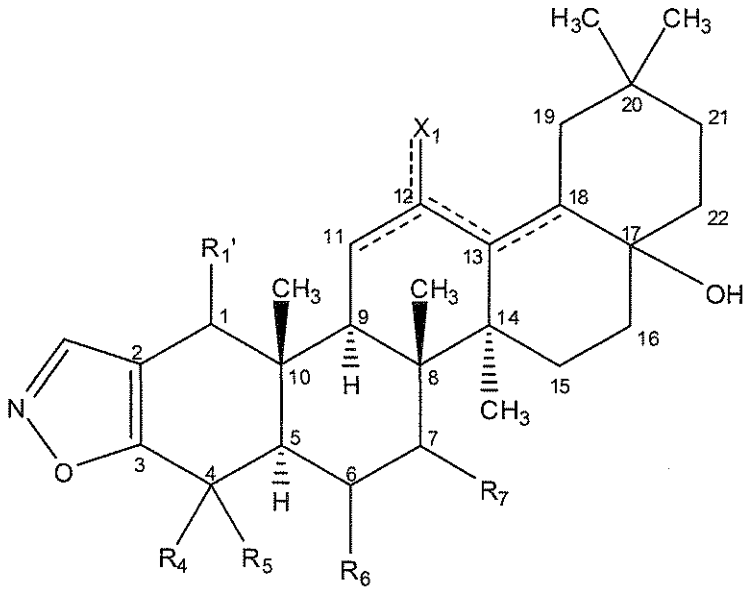


or salts, hydrates, solvates, tautomers, or optical isomers thereof. In certain ~~embodiments~~examples, the following particular compound is contemplated:



or salts thereof, and substantially free from other optical isomers thereof.

A further example~~embodiment~~ contemplated by the present disclosure is A compound of the formula:

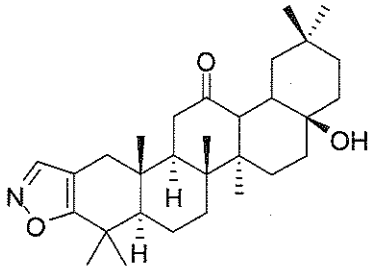


(XII),

wherein: X_1 is hydrogen, 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; 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_4 and R_5 are each independently $alkyl_{(C\leq8)}$ or substituted $alkyl_{(C\leq8)}$; and R_6 and R_7 are each independently hydrogen or hydroxy; or salts, esters, hydrates, solvates, tautomers, or optical isomers thereof.

In certain ~~embodiments~~examples regarding compounds comprising X_1, X_1 is OR_b and R_b is absent. In certain ~~embodiments~~examples regarding compounds comprising R_4 and R_5, R_4 and R_5 are each independently $alkyl_{(C\leq4)}$. For example, R_4 and R_5 are each methyl in certain ~~embodiments~~examples. In certain ~~embodiments~~examples regarding compounds comprising R_6 and R_7, R_6 and R_7 are each hydrogen. In certain ~~embodiments~~examples regarding compounds comprising a bond between carbons 13 and 18, the bond joining carbon 13 and carbon 18 is a single bond.

In particular ~~embodiments~~examples, the compound of formula (XII) is further defined as:



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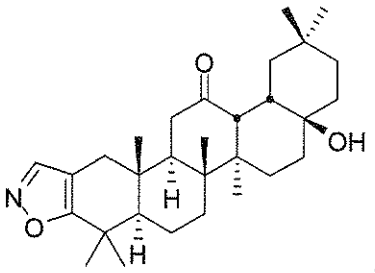
or salts, hydrates, solvates, tautomers, or optical isomers thereof. In certain examplembodiments, the following particular compound is contemplated:



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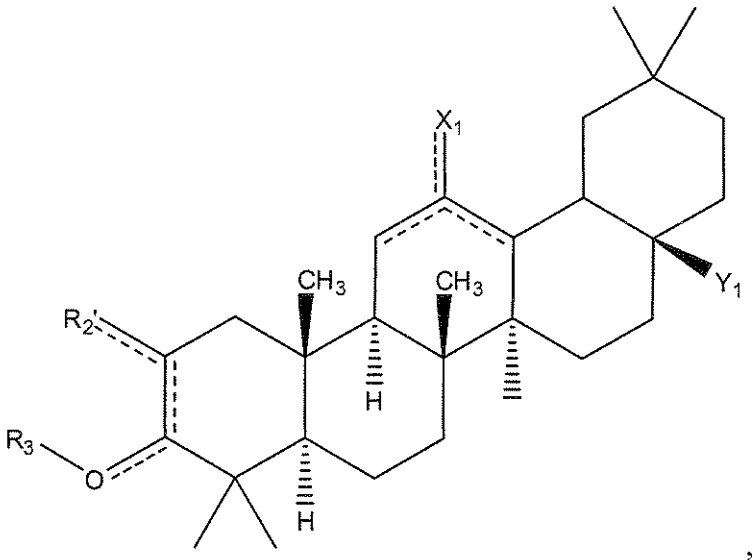
or salts thereof, and substantially free from other optical isomers thereof.

Another general aspect of the present disclosure contemplates a compound of the formula:

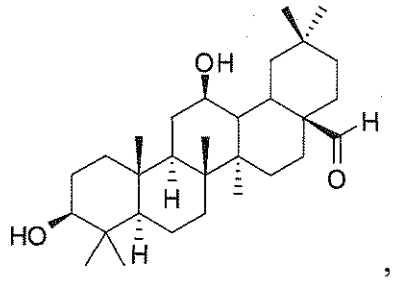


, (XIII)

wherein: X_1 is $-OR_b$, wherein R_b is hydrogen: provided that R_b is absent when the oxygen atom to which it is bound is part of a double bond, further provided that when R_b is absent the oxygen atom to which it is bound is part of a double bond; Y_1 is hydroxy, –CHO, or –OC(O)H: R_2' is hydrogen or –C(H)(OH); R_3 is absent or hydrogen; provided that R_3 is absent when the oxygen atom to which it is bound is part of a double bond, further provided

that when R_3 is absent the oxygen atom to which it is bound is part of a double bond; or salts, esters, hydrates, solvates, tautomers, or optical isomers thereof.

In particular example~~embodiments~~, the compound of formula (XIII) is further defined as:



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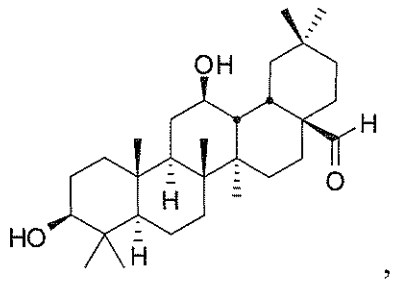
or salts, hydrates, solvates, tautomers, or optical isomers thereof. In certain example~~embodiments~~, the following particular compound is contemplated:



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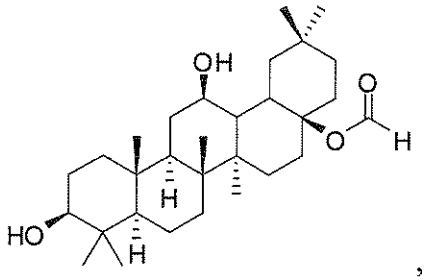
or salts thereof, and substantially free from other optical isomers thereof. In certain example~~embodiments~~, the following compound is contemplated:



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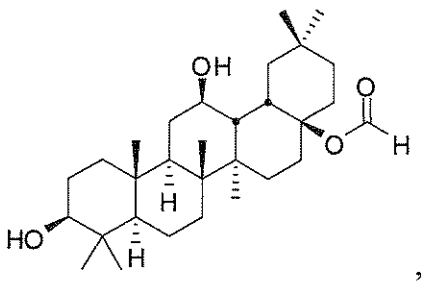
or salts, hydrates, solvates, tautomers, or optical isomers thereof. In certain example~~embodiments~~, the following particular compound is contemplated:



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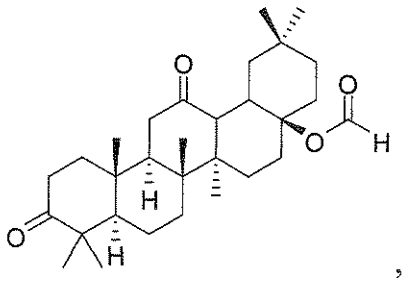
or salts thereof, and substantially free from other optical isomers thereof. In certain example~~embodiments~~, the following compound is contemplated:



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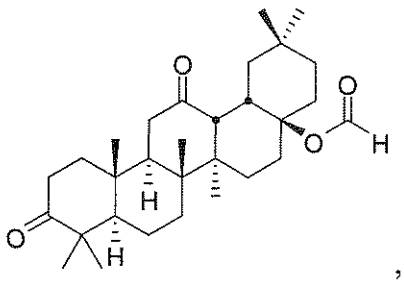
or salts, hydrates, solvates, tautomers, or optical isomers thereof. In certain example~~embodiments~~, the following particular compound is contemplated:



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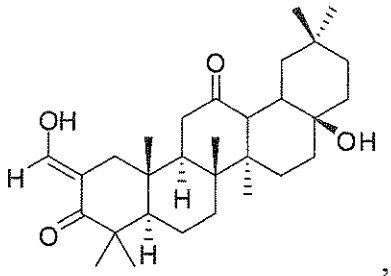
or salts thereof, and substantially free from other optical isomers thereof. In certain example~~embodiments~~, the following compound is contemplated:



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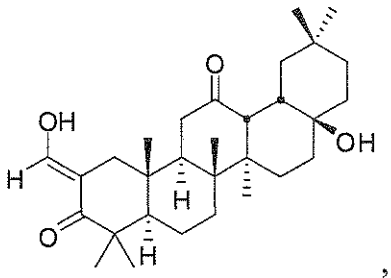
or salts, hydrates, solvates, tautomers, or optical isomers thereof. In certain example~~embodiments~~, the following particular compound is contemplated:



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or salts thereof, and substantially free from other optical isomers thereof.

In some ~~embodiments~~examples, compounds of the present disclosure are in the form of pharmaceutically acceptable salts. In other ~~embodiments~~examples, compounds of the present disclosure are not be in the form of a salt. In certain ~~embodiments~~examples, a compound of the present disclosure is a hydrate. In other ~~embodiments~~examples, a compound of the present disclosure is not a hydrate. In certain ~~embodiments~~examples, a compound of the present disclosure is a solvate. In other ~~embodiments~~examples, a compound of the present disclosure is not a solvate.

In some ~~embodiments~~examples, compounds of the present disclosure can be esters of the above formulas. The ester may, for example, result from a condensation reaction between a hydroxy group of the formula and the carboxylic acid group of biotin. In certain ~~embodiments~~examples, a compound of the present disclosure is not an ester.

In some ~~embodiments~~examples, the compounds of the present disclosure can be present as a mixture of stereoisomers. In certain ~~embodiments~~examples, compounds of the present disclosure are present as predominantly one optical isomer. In other ~~embodiments~~examples, the compounds of the present disclosure are present as single stereoisomers.

In some ~~embodiments~~examples, compounds of the present disclosure may be inhibitors of IFN-γ-induced nitrous oxide (NO) production in macrophages, for example, having an IC_{50} value of less than 0.2 μM.

Other general aspects of the present disclosure contemplate a pharmaceutical composition comprising as an active ingredient a compound of the present disclosure and a pharmaceutically acceptable carrier. The composition may, for example, be adapted for administration by a route selected from the group consisting of orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularally, intrapericardially, intraperitoneally, intrapleurally, intraprostaticaly, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, orally, 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, via localized perfusion, bathing target cells directly, or any combination thereof. In particular ~~embodiments~~examples, the composition may be formulated for oral delivery. In particular ~~embodiments~~examples, the composition is formulated as a hard or soft capsule, a tablet, a syrup, a suspension, a wafer, or an elixir. In certain ~~embodiments~~examples, the soft capsule is a gelatin capsule. Certain compositions may comprise a protective coating, such as those compositions

formulated for oral delivery. Certain compositions further comprise an agent that delays absorption, such as those compositions formulated for oral delivery. Certain compositions may further comprise an agent that enhances solubility or dispersibility, such as those compositions formulated for oral delivery. Certain compositions may comprise a compound of the present disclosure, wherein the compound is dispersed in a liposome, an oil and water emulsion or a water and oil emulsion.

Yet another general exampleaspect of the present disclosure contemplates a therapeutic method comprising administering a pharmaceutically effective amount of a compound of the present disclosure to a subject. The subject may, for example, be a human. These or any other methods of the present disclosure may further comprise identifying a subject in need of treatment.

Another method of the present disclosure contemplates a method of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure. The cancer may be any type of cancer, such as a carcinoma, sarcoma, lymphoma, leukemia, melanoma, mesothelioma, multiple myeloma, or seminoma. Other types of cancers include cancer of the bladder, blood, bone, brain, breast, central nervous system, colon, endometrium, esophagus, genitourinary tract, head, larynx, liver, lung, neck, ovary, pancreas, prostate, spleen, small intestine, large intestine, stomach, or testicle. In these or any other methods, the subject may be a primate. This or any other method may further comprise identifying a subject in need of treatment. The subject may have a family or patient history of cancer. In certain exampleembodiments, the subject has symptoms of cancer. The compounds of the disclosureinvention may be administered *via* any method described herein, such as locally. In certain exampleembodiments, the compound is administered by direct intratumoral injection or by injection into tumor vasculature. In certain exampleembodiments, the compounds may be administered systemically. The compounds may be administered intravenously, intra-arterially, intramuscularly, intraperitoneally, subcutaneously or orally, in certain embodiments.

In certain exampleembodiments regarding methods of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the pharmaceutically effective amount is 0.1 – 1000 mg/kg. In certain exampleembodiments, the pharmaceutically effective amount is administered in a single dose per day. In certain exampleembodiments, the pharmaceutically effective amount is administered in two or more doses per day. The compound may be administered by contacting a tumor cell during *ex vivo* purging, for example. The method of treatment may comprise any one or more of the

following: a) inducing cytotoxicity in a tumor cell; b) killing a tumor cell; c) inducing apoptosis in a tumor cell; d) inducing differentiation in a tumor cell; or e) inhibiting growth in a tumor cell. The tumor cell may be any type of tumor cell, such as a leukemia cell. Other types of cells include, for example, a bladder cancer cell, a breast cancer cell, a lung cancer cell, a colon cancer cell, a prostate cancer cell, a liver cancer cell, a pancreatic cancer cell, a stomach cancer cell, a testicular cancer cell, a brain cancer cell, an ovarian cancer cell, a lymphatic cancer cell, a skin cancer cell, a brain cancer cell, a bone cancer cell, or a soft tissue cancer cell.

Combination treatment therapy is also contemplated by the present disclosure. For example, regarding methods of treating cancer in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the method may further comprise a treatment selected from the group consisting of administering a pharmaceutically effective amount of a second drug, radiotherapy, gene therapy, and surgery. Such methods may further comprise (1) contacting a tumor cell with the compound prior to contacting the tumor cell with the second drug, (2) contacting a tumor cell with the second drug prior to contacting the tumor cell with the compound, or (3) contacting a tumor cell with the compound and the second drug at the same time. The second drug may, in certain example~~embodiments~~, be an antibiotic, anti-inflammatory, anti-neoplastic, anti-proliferative, anti-viral, immunomodulatory, or immunosuppressive. The second drug may be an alkylating agent, androgen receptor modulator, cytoskeletal disruptor, estrogen receptor modulator, histone-deacetylase inhibitor, HMG-CoA reductase inhibitor, prenyl-protein transferase inhibitor, retinoid receptor modulator, topoisomerase inhibitor, or tyrosine kinase inhibitor. In certain example~~embodiments~~, the second drug is 5-azacitidine, 5-fluorouracil, 9-cis-retinoic acid, actinomycin D, alitretinoin, all-trans-retinoic acid, annamycin, axitinib, belinostat, bevacizumab, bexarotene, bosutinib, busulfan, capecitabine, carboplatin, carmustine, CD437, cediranib, cetuximab, chlorambucil, cisplatin, cyclophosphamide, cytarabine, dacarbazine, dasatinib, daunorubicin, decitabine, docetaxel, dolastatin-10, doxifluridine, doxorubicin, doxorubicin, epirubicin, erlotinib, etoposide, etoposide, gefitinib, gemcitabine, gemtuzumab ozogamicin, hexamethylmelamine, idarubicin, ifosfamide, imatinib, irinotecan, isotretinoin, ixabepilone, lapatinib, LBH589, lomustine, mechlorethamine, melphalan, mercaptopurine, methotrexate, mitomycin, mitoxantrone, MS-275, neratinib, nilotinib, nitrosourea, oxaliplatin, paclitaxel, plicamycin, procarbazine, semaxanib, semustine, sodium butyrate, sodium phenylacetate, streptozotocin, suberoylanilide hydroxamic acid, sunitinib, tamoxifen, teniposide, thiopeta, tioguanine,

topotecan, TRAIL, trastuzumab, tretinoin, trichostatin A, valproic acid, valrubicin, vandetanib, vinblastine, vincristine, vindesine, or vinorelbine.

Methods of treating or preventing a disease with an inflammatory component in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. The disease may be, for example, lupus or rheumatoid arthritis. The disease may be an inflammatory bowel disease, such as Crohn's disease or ulcerative colitis. The disease with an inflammatory component may be a cardiovascular disease. The disease with an inflammatory component may be diabetes, such as type 1 or type 2 diabetes. Compounds of the present disclosure may also be used to treat complications associated with diabetes. Such complications are well-known in the art and include, for example, obesity, hypertension, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, myonecrosis, retinopathy and metabolic syndrome (syndrome X). The disease with an inflammatory component may be a skin disease, such as psoriasis, acne, or atopic dermatitis. Administration of a compound of the present disclosure in treatment methods of such skin diseases may be, for example, topical or oral.

The disease with an inflammatory component may be metabolic syndrome (syndrome X). A patient having this syndrome is characterized as having three or more symptoms selected from the following group of five symptoms: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low high-density lipoprotein cholesterol (HDL); (4) high blood pressure; and (5) elevated fasting glucose, which may be in the range characteristic of Type 2 diabetes if the patient is also diabetic. Each of these symptoms is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670, incorporated herein by reference. Patients with metabolic syndrome, whether or not they have or develop overt diabetes mellitus, have an increased risk of developing the macrovascular and microvascular complications that are listed above that occur with type 2 diabetes, such as atherosclerosis and coronary heart disease.

Another general <u>example</u>~~method~~ of the present disclosure entails a method of treating or preventing a cardiovascular disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure. The cardiovascular disease may be, for example, atherosclerosis, cardiomyopathy, congenital heart disease, congestive heart failure, myocarditis, rheumatic heart disease, valve disease,

coronary artery disease, endocarditis, or myocardial infarction. Combination therapy is also contemplated for such methods. For example, such methods may further comprise administering a pharmaceutically effective amount of a second drug. The second drug may be, for example, a cholesterol lowering drug, an anti-hyperlipidemic, a calcium channel blocker, an anti-hypertensive, or an HMG-CoA reductase inhibitor. Non-limiting examples of second drugs include amlodipine, aspirin, ezetimibe, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine or nitrendipine. Other non-limiting examples of second drugs include atenolol, bucindolol, carvedilol, clonidine, doxazosin, indoramin, labetalol, methyldopa, metoprolol, nadolol, oxprenolol, phenoxybenzamine, phentolamine, pindolol, prazosin, propranolol, terazosin, timolol or tolazoline. The second drug may be, for example, a statin, such as atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin or simvastatin.

Methods of treating or preventing a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. The neurodegenerative disease may, for example, be selected from the group consisting of Parkinson's disease, Alzheimer's disease, multiple sclerosis (MS), Huntington's disease and amyotrophic lateral sclerosis. In particular example~~embodiments~~, the neurodegenerative disease is Alzheimer's disease. In particular example~~embodiments~~, the neurodegenerative disease is MS, such as primary progressive, relapsing-remitting secondary progressive or progressive relapsing MS. The subject may be, for example, a primate. The subject may be a human.

In particular example~~embodiments~~ of methods of treating or preventing a neurodegenerative disease in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the treatment suppresses the demyelination of neurons in the subject's brain or spinal cord. In certain example~~embodiments~~, the treatment suppresses inflammatory demyelination. In certain example~~embodiments~~, the treatment suppresses the transection of neuron axons in the subject's brain or spinal cord. In certain example~~embodiments~~, the treatment suppresses the transection of neurites in the subject's brain or spinal cord. In certain example~~embodiments~~, the treatment suppresses neuronal apoptosis in the subject's brain or spinal cord. In certain example~~embodiments~~, the treatment stimulates the remyelination of neuron axons in the subject's brain or spinal cord. In certain example~~embodiments~~, the treatment restores lost function after an MS attack. In certain example~~embodiments~~, the treatment prevents a new MS attack. In certain example~~embodiments~~, the treatment prevents a disability resulting from an MS attack.

One general exampleaspect of the present disclosure contemplates a method of treating or preventing a disorder characterized by overexpression of iNOS genes in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure.

Another general exampleaspect of the present disclosure contemplates a method of inhibiting IFN-γ-induced nitric oxide production in cells of a subject, comprising administering to said subject a pharmaceutically effective amount of a compound of the present disclosure.

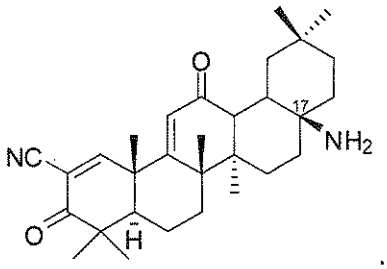
Yet another general examplemethod of the present disclosure contemplates a method of treating or preventing a disorder characterized by overexpression of COX-2 genes in a subject, comprising administering to the subject a pharmaceutically effective amount of compound of the present disclosure.

Methods of treating renal/kidney disease (RKD) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure are also contemplated. See U.S. Patent Application 12/352,473, which is incorporated by reference herein in its entirety. The RKD may result from, for example, a toxic insult. The toxic insult may result from, for example, an imaging agent or a drug. The drug may be a chemotherapeutic, for example. The RKD may result from ischemia/reperfusion injury, in certain examplembodiments. In certain examplembodiments, the RKD results from diabetes or hypertension. The RKD may result from an autoimmune disease. The RKD may be further defined as chronic RKD, or acute RKD.

In certain examplemethods of treating renal/kidney disease (RKD) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure, the subject has undergone or is undergoing dialysis. In certain examplembodiments, the subject has undergone or is a candidate to undergo kidney transplant. The subject may be a primate. The primate may be a human. The subject in this or any other method may be, for example, a cow, horse, dog, cat, pig, mouse, rat or guinea pig.

Also contemplated by the present disclosure is a method for improving glomerular filtration rate or creatinine clearance in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound of the present disclosure.

Methods of synthesizing compounds of the present disclosure are also contemplated. In particular examplembodiments, such methods comprise a method of making a first compound defined as:



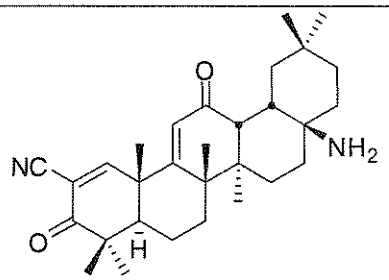
Kits are also contemplated by the present disclosure, such as a kit comprising: a compound of the present disclosure; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the compound is to be administered, storage information for the compound, dosing information and instructions regarding how to administer the compound. The kit may comprise a compound of the present disclosure in a multiple dose form.

Other general exampleaspects of the present disclosure contemplate articles of manufacture. For example, an article of manufacture may comprise a compound of the present disclosure; and packaging materials. The packaging materials may comprise a container for housing the compound, in certain exampleembodiments. The container may comprise, for example, a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound. In certain exampleembodiments, the article of manufacture comprises the compound in a multiple dose form.

In some exampleembodiments, the disclosureinvention provides compounds that may prevent and/or treat diseases or disorders whose pathology involves oxidative stress, inflammation, and/or dysregulation of inflammatory signaling pathways. In some variations, the diseases or disorders can be characterized by overexpression of inducible nitric oxide synthase (iNOS) and/or inducible cyclooxygenase (COX-2) in affected tissues. In some variations, the diseases or disorders can be characterized by overproduction of reactive oxygen species (ROS) or reactive nitrogen species (RNS) such as superoxide, hydrogen peroxide, nitric oxide or peroxynitrite in affected tissues. In some variations, the disease or disorder is characterized by excessive production of inflammatory cytokines or other inflammation-related proteins such as TNFα, IL-6, IL-1, IL-8, ICAM-1, VCAM-1, and VEGF. Such diseases or disorders may, in some exampleembodiments, involve undesirable proliferation of certain cells, as in the case of cancer (*e.g.*, solid tumors, leukemias, myelomas, lymphomas, and other cancers), fibrosis associated with organ failure, or excessive scarring. Non limiting examples of the disease or disorder include: lupus, rheumatoid arthritis, juvenile-onset diabetes,

multiple sclerosis, psoriasis, and Crohn's disease. Further non-limiting examples include cardiovascular diseases, such as atherosclerosis, heart failure, myocardial infarction, acute coronary syndrome, restenosis following vascular surgery, hypertension, and vasculitis; neurodegenerative or neuromuscular diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, and muscular dystrophy; neurological disorders such as epilepsy and dystonia; neuropsychiatric conditions such as major depression, bipolar disorder, post-traumatic stress disorder, schizophrenia, anorexia nervosa, ADHD, and autism-spectrum disorders; retinal diseases such as macular degeneration, diabetic retinopathy, glaucoma, and retinitis; chronic and acute pain syndromes, including inflammatory and neuropathic pain; hearing loss and tinnitus; diabetes and complications of diabetes, including metabolic syndrome, diabetic nephropathy, diabetic neuropathy, and diabetic ulcers; respiratory diseases such as asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, and cystic fibrosis; inflammatory bowel diseases; osteoporosis, osteoarthritis, and other degenerative conditions of bone and cartilage; acute or chronic organ failure, including renal failure, liver failure (including cirrhosis and hepatitis), and pancreatitis; ischemia-reperfusion injury associated with thrombotic or hemorrhagic stroke, subarachnoid hemorrhage, cerebral vasospasm, myocardial infarction, shock, or trauma; complications of organ or tissue transplantation including acute or chronic transplant failure or rejection and graft-versus-host disease; skin diseases including atopic dermatitis and acne; sepsis and septic shock; excessive inflammation associated with infection, including respiratory inflammation associated with influenza and upper respiratory infections; mucositis associated with cancer therapy, including radiation therapy or chemotherapy; and severe burns.

Non-limiting examples of compounds describedisclosed herein include:



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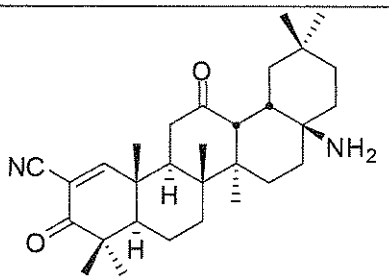

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