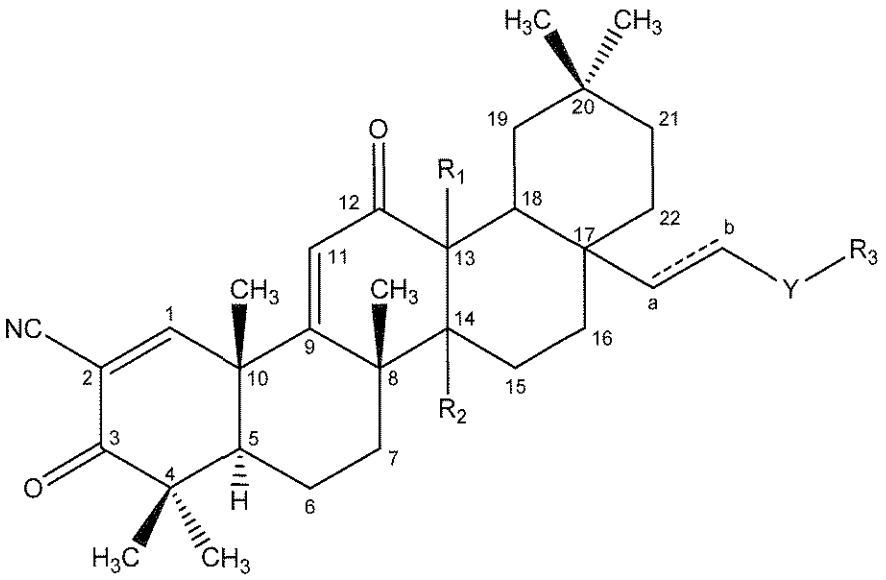
compounds have been less extensively characterized (Honda *et al.*, 2006). The pharmacology of these synthetic triterpenoid molecules is complex. Compounds derived from oleanolic acid have been shown to affect the function of multiple protein targets and thereby modulate the activity of several important cellular signaling pathways related to oxidative stress, cell cycle control, and inflammation (*e.g.*, Dinkova-Kostova *et al.*, 2005; Ahmad *et al.*, 2006; Ahmad *et al.*, 2008; Liby *et al.*, 2007a). Derivatives of betulinic acid, though they have shown comparable anti-inflammatory properties, also appear to have significant differences in their pharmacology compared to OA-derived compounds (Liby *et al.*, 2007b). Given that the biological activity profiles of known triterpenoid derivatives vary, and in view of the wide variety of diseases that may be treated or prevented with compounds having potent antioxidant and anti-inflammatory effects, and the high degree of unmet medical need represented within this variety of diseases, it is desirable to synthesize new compounds with diverse structures that may have improved biological activity profiles for the treatment of one or more indications.

SUMMARY ~~OF THE INVENTION~~

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

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



(I),

wherein:

Y is a covalent bond, $-CH_2-$, $-C(O)-$, $-O-$, or $-NH-$;

R_1 and R_2 are each independently −H, −OH, methyl, or as defined below; and

R_3 is:

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

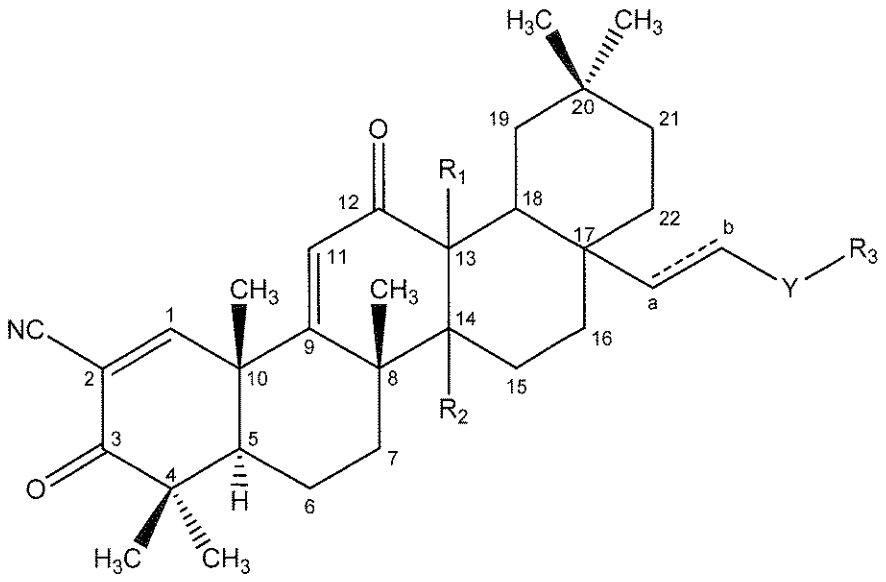
$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $heterocycloalkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $alkoxyamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $heterocycloalkylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, −NH−$amido_{(C\leq 8)}$, or a substituted version of any of these groups;

R_3 and R_1, taken together, are −O−, $-NR_a-$ or a covalent bond between Y and carbon atom 13, wherein R_a is hydrogen or $alkyl_{(C\leq 4)}$; or

R_3 and R_2, taken together, are −O−, $-NR_a-$ or a covalent bond between Y and carbon atom 14, wherein R_a is hydrogen or $alkyl_{(C\leq 4)}$;

or a pharmaceutically acceptable salt thereof.

In some ~~embodiments~~examples, the compounds are further defined as:



(I),

wherein:

Y is $-CH_2-$, −C(O)−, −O−, or −NH−;

R_1 and R_2 are each independently −H, −OH, methyl, or as defined below; and

R_3 is:

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

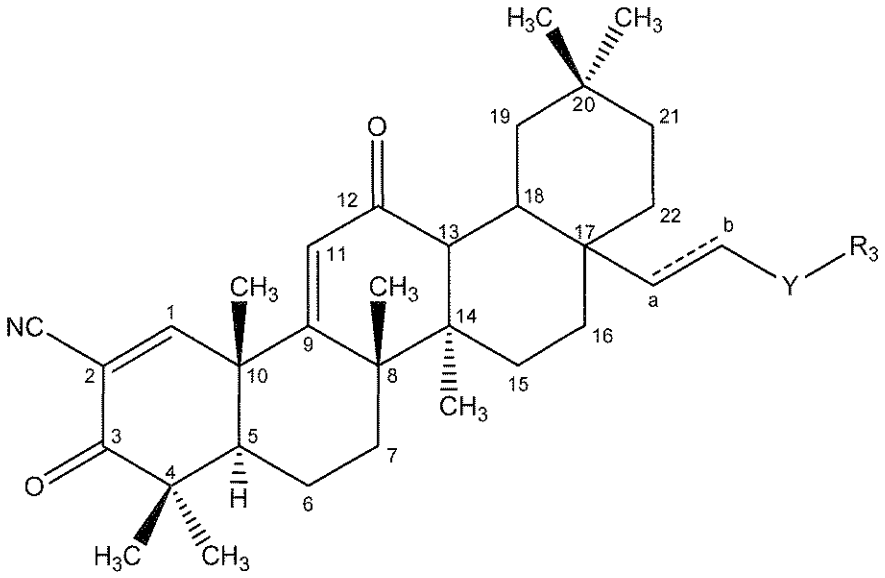
$alkyl_{(C\leq 8)}$, $alkenyl_{(C\leq 8)}$, $alkynyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $aralkyl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $alkenyloxy_{(C\leq 8)}$, $aryloxy_{(C\leq 8)}$, $aralkoxy_{(C\leq 8)}$, $heteroaryloxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $heterocycloalkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkenylamino_{(C\leq 8)}$, $alkoxyamino_{(C\leq 8)}$, $arylamino_{(C\leq 8)}$, $aralkylamino_{(C\leq 8)}$, $heteroarylamino_{(C\leq 8)}$, $heterocycloalkylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, $amido_{(C\leq 8)}$, –NH–$amido_{(C\leq 8)}$, or a substituted version of any of these groups;

R_3 and R_1, taken together, are –O–, $-NR_a-$ or a covalent bond between Y and carbon atom 13, wherein R_a is hydrogen or $alkyl_{(C\leq 4)}$; or

R_3 and R_2, taken together, are –O–, $-NR_a-$ or a covalent bond between Y and carbon atom 14, wherein R_a is hydrogen or $alkyl_{(C\leq 4)}$;

or a pharmaceutically acceptable salt thereof.

In some ~~embodiments~~examples, the compounds are further defined as:



(II),

wherein:

Y is a covalent bond, $-CH_2-$, –C(O)–, –O–, or –NH–; and

R_3 is:

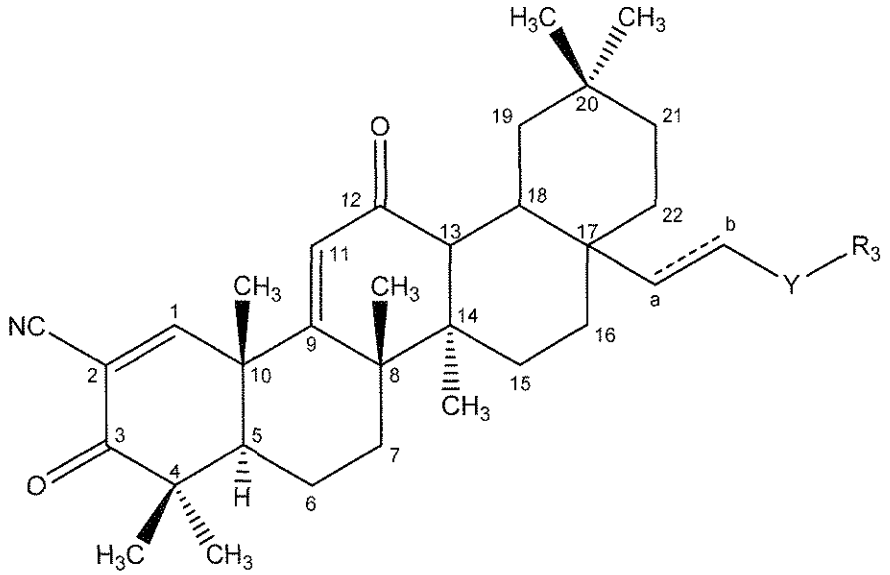
hydrogen, hydroxy, halo, amino, –NHOH, or mercapto; or

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

aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, heterocycloalkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, alkoxyamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, heterocycloalkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –NH–amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt thereof.

In some ~~embodiments~~examples, the compounds are further defined as:



(II),

wherein:

Y is –CH_2–, –C(O)–, –O–, or –NH–; and

R_3 is:

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

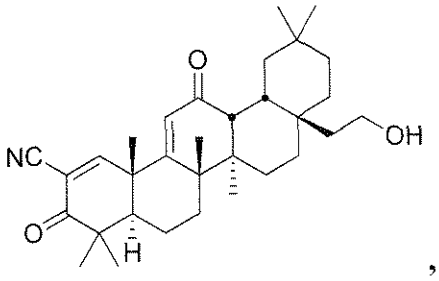
alkyl$_{(C\leq 8)}$, alkenyl$_{(C\leq 8)}$, alkynyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, aralkyl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, alkenyloxy$_{(C\leq 8)}$, aryloxy$_{(C\leq 8)}$, aralkoxy$_{(C\leq 8)}$, heteroaryloxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, heterocycloalkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, alkoxyamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, heterocycloalkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –NH–amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt thereof.

In some ~~embodiments~~examples, the bond between carbon atoms a and b is a single bond. In some ~~embodiments~~examples, the bond between carbon atoms a and b is a double bond. In some ~~embodiments~~examples, Y is a covalent bond. In some ~~embodiments~~examples, Y is $-CH_2-$. In some ~~embodiments~~examples, Y is $-C(O)-$. In some ~~embodiments~~examples, Y is $-O-$. In some ~~embodiments~~examples, R_1 is $-H$. In some ~~embodiments~~examples, R_2 is methyl.

In some examples~~embodiments~~, R_3 is $-H$. In some examples~~embodiments~~, R_3 is $-OH$. In some examples~~embodiments~~, R_3 is amino. In some examples~~embodiments~~, R_3 is $alkyl_{(C\leq 8)}$, for example methyl. In some examples~~embodiments~~, R_3 is $heterocycloalkyl_{(C\leq 8)}$, for example, morpholinyl, pyrrolidinyl, azetidinyl or piperazinyl. In some examples~~embodiments~~, R_3 is substituted $heterocycloalkyl_{(C\leq 8)}$, for example, hydroxypyrrolidinyl, difluoropyrrolidinyl, hydroxypiperidinyl, or *N*-Boc-piperazinyl. In some examples~~embodiments~~, R_3 is $acyl_{(C\leq 8)}$, for example, acetyl. In some examples~~embodiments~~, R_3 is substituted $acyl_{(C\leq 8)}$, for example, ethylaminocarbonyl. In some examples~~embodiments~~, R_3 is $alkoxy_{(C\leq 8)}$, for example, methoxy, ethoxy, isopropoxy, *tert*-butoxy, or $-O-$cyclohexyl. In some examples~~embodiments~~, R_3 is $aryloxy_{(C\leq 8)}$, for example, $-O-$phenyl. In some examples~~embodiments~~, R_3 is $aralkoxy_{(C\leq 8)}$, for example, benzyloxy. In some examples~~embodiments~~, R_3 is substituted $acyloxy_{(C\leq 8)}$, for example, $-OC(O)NHCH_2CH_3$. In some examples~~embodiments~~, R_3 is $heterocycloalkoxy_{(C\leq 8)}$, for example, $-O-$piperidinyl or *N*-Boc-piperidinyloxy. In some examples~~embodiments~~, R_3 is $alkylamino_{(C\leq 8)}$, for example, methylamino, ethylamino, isopropylamino, *tert*-butylamino or cyclohexylamino. In some examples~~embodiments~~, R_3 is substituted $alkylamino_{(C\leq 8)}$, for example, 2,2,2-trifluoroethylamino, $-NHCH_2C(O)OCH_3$ or $-NHCH_2C(O)OH$. In some examples~~embodiments~~, R_3 is $dialkylamino_{(C\leq 8)}$, for example, dimethylamino. In some examples~~embodiments~~, R_3 is $alkoxyamino_{(C\leq 8)}$, for example, methoxyamino. In some examples~~embodiments~~, R_3 is $arylamino_{(C\leq 8)}$, for example, phenylamino. In some examples~~embodiments~~, R_3 is $aralkylamino_{(C\leq 8)}$, for example, benzylamino. In some examples~~embodiments~~, R_3 is $heteroarylamino_{(C\leq 8)}$, for example, pyridinylamino. In some examples~~embodiments~~, R_3 is $heterocycloalkylamino_{(C\leq 8)}$, for example, oxetanylamino. In some examples~~embodiments~~, R_3 is $-NH-amido_{(C\leq 8)}$, for example, $-NHNHC(O)CH_3$.

In some examples~~embodiments~~, the compounds are selected from the groups comprising:



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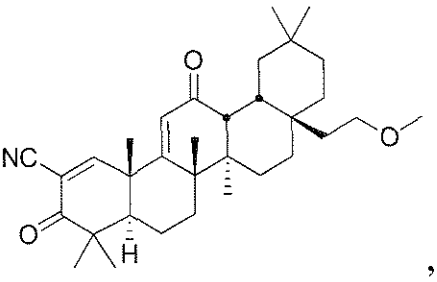

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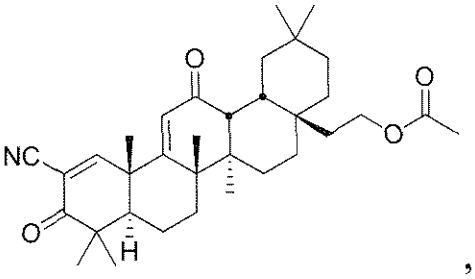

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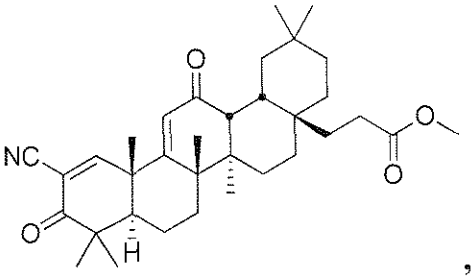

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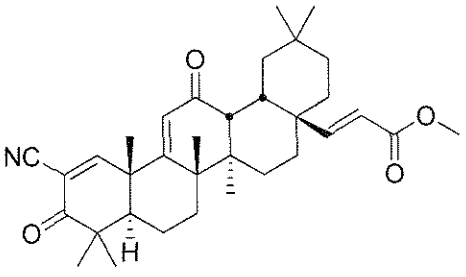

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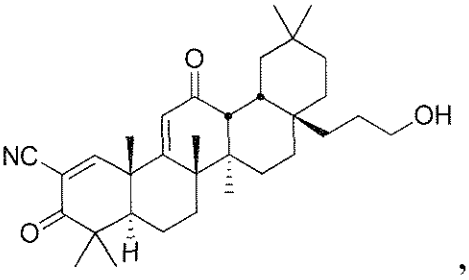

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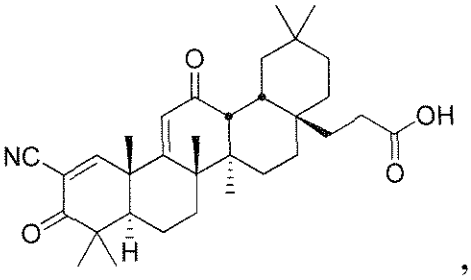

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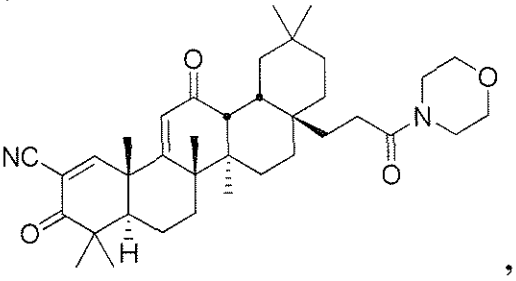

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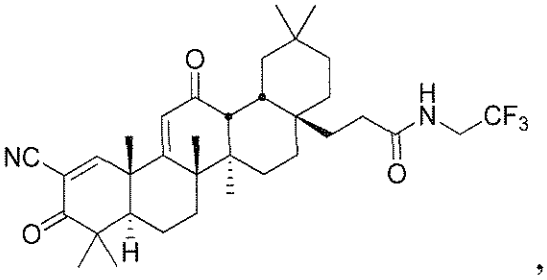

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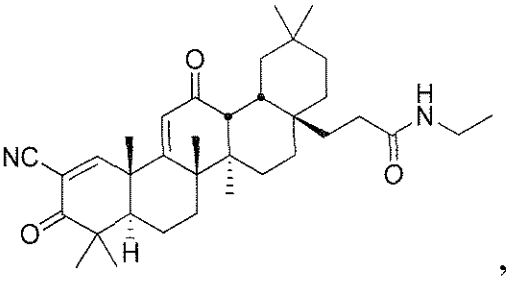

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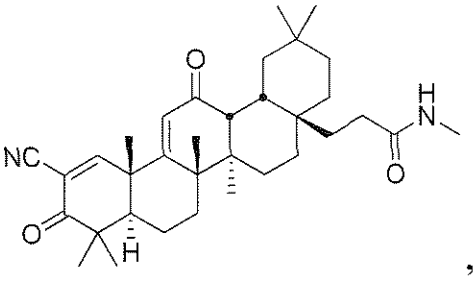

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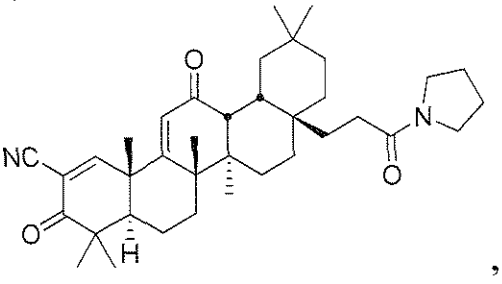


,

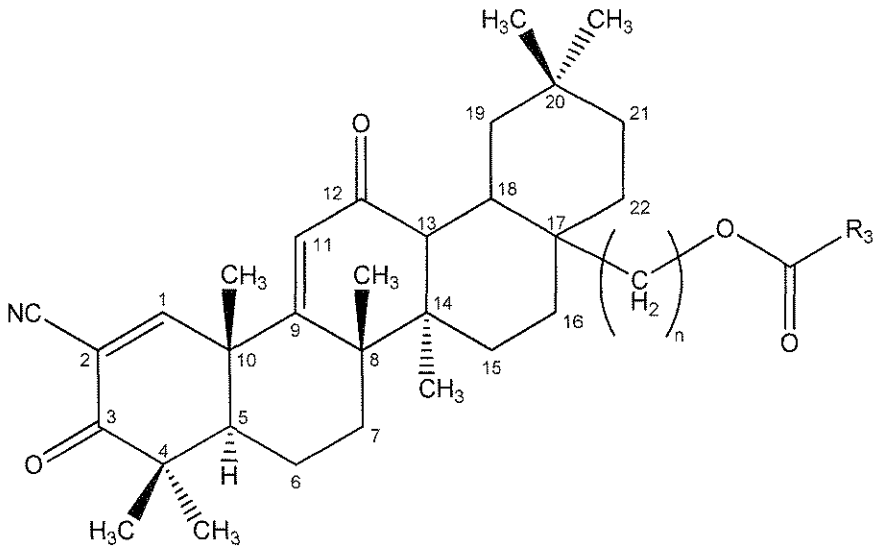
alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –NH–amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_3 and R_1, taken together, are $-NR_a-$, wherein R_a is hydrogen or alkyl$_{(C\leq 4)}$; or

R_3 and R_2, taken together, are $-NR_a-$, wherein R_a is hydrogen or alkyl$_{(C\leq 4)}$; or

or a pharmaceutically acceptable salt thereof.

In some examples~~embodiments~~, the compounds are further defined as:



(IV),

wherein:

n is 1 to 6; and

R_3 is:

amino or –NHOH; or

N-heteroaryl$_{(C\leq 8)}$, *N*-heterocycloalkyl$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkenylamino$_{(C\leq 8)}$, alkoxyamino$_{(C\leq 8)}$, arylamino$_{(C\leq 8)}$, aralkylamino$_{(C\leq 8)}$, heteroarylamino$_{(C\leq 8)}$, heterocycloalkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, –NH–amido$_{(C\leq 8)}$, or a substituted version of any of these groups;

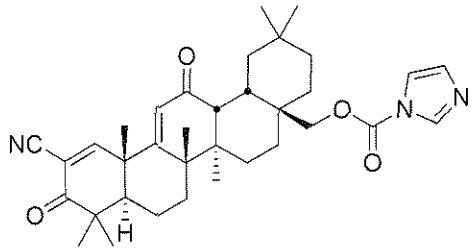
or a pharmaceutically acceptable salt thereof.

In some examples~~embodiments~~, n is 1. In other examples~~embodiments~~, n is 2. In still other embodiments, n is 3.

In some examples~~embodiments~~, R_1 is –H. In some examples~~embodiments~~, R_2 is methyl.

In some examples~~embodiments~~, R_3 is *N*-heteroaryl$_{(C\leq 8)}$, for example, imidazolyl. In some examples~~embodiments~~, R_3 is *N*-heterocycloalkyl$_{(C\leq 8)}$, for example, morpholinyl or pyrrolidinyl. In some examples~~embodiments~~, R_3 is alkylamino$_{(C\leq 8)}$, for example, ethylamino.

In some examples~~embodiments~~, the compounds are selected from the groups comprising:



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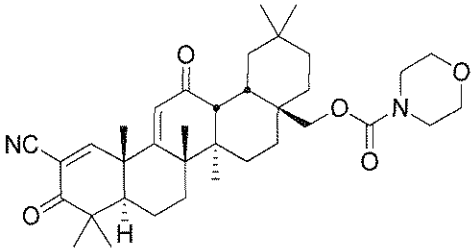

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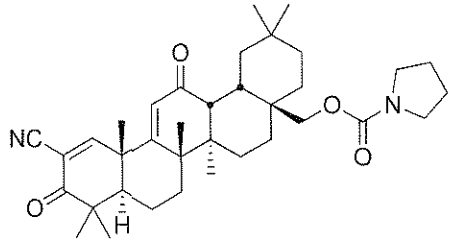

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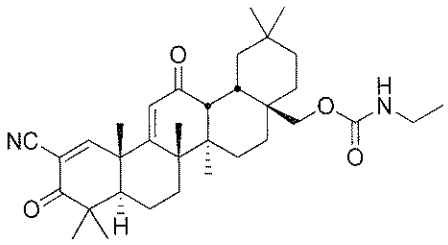

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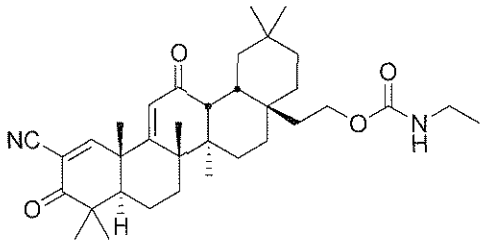

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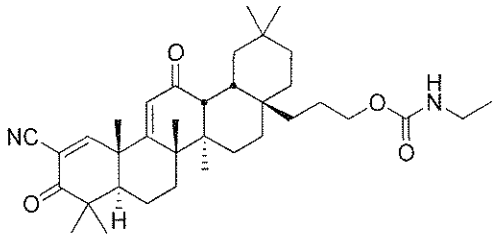

,

or a pharmaceutically acceptable salt thereof.

In some examples~~aspects~~, there are ~~provided~~described ~~-~~pharmaceutical compositions comprising one or more of the above compounds and an excipient. In one aspect, the present invention refers to use of a compound as previously described in the manufacture of a medicament for treating and/or preventing a disease or a disorder in a patient in need thereof. In other examples~~aspects~~ there are ~~provided~~ described methods of treating and/or preventing a disease or a disorder in patients in need thereof, comprising administering to such patients one or more of the above compounds in an amount sufficient to treat and/or prevent the disease or disorder.

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

b) an excipient.

70. Use of a compound according to any one of claims 1-68 in the manufacture of a medicament for~~A method of~~ treating and/or preventing a disease or a disorder in a patient in need thereof~~, comprising administering to the patient a compound according to any one of claims 1-68 in an amount sufficient to treat and/or prevent the disease or disorder~~.