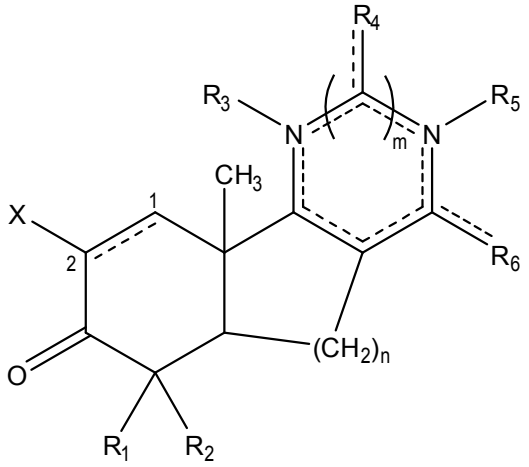
SUMMARY

The present disclosure describes novel compounds, including pyrazolyl and pyrimidinyl tricyclic enones with anti-inflammatory and/or antioxidant properties, pharmaceutical compositions thereof, methods for their manufacture, and methods for their use.

The present invention refers to subject matter as defined in the attached set of claims.

In one example of the present disclosure there are disclosed compounds of the formula:



(I),

wherein:

the atoms labeled 1 and 2 are connected either by a double bond or an epoxidized double bond;

n is 1 or 2;

m is 0 or 1;

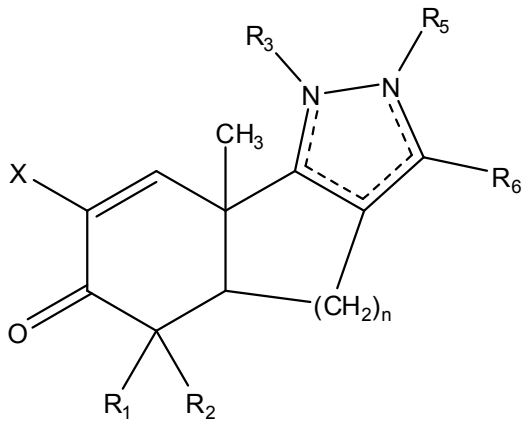
X is −CN, $-CF_3$, or $-C(O)R_a$, wherein R_a is −OH, $alkoxy_{(C\leq6)}$, $alkylamino_{(C\leq6)}$, $dialkylamino_{(C\leq6)}$, or $-NHS(O)_2-alkyl_{(C1-4)}$;

R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

oxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(II),

wherein:

n is 1 or 2;

X is −CN, −CF_3, or −C(O)R_a, wherein R_a is −OH, alkoxy$_{(C\leq6)}$, alkylamino$_{(C\leq6)}$, dialkylamino$_{(C\leq6)}$, or −$NHS(O)_2$−alkyl$_{(C1\text{-}4)}$;

R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq12)}$, alkenediyl$_{(C\leq12)}$, alkoxydiyl$_{(C\leq12)}$, alkylaminodiyl$_{(C\leq12)}$, or a substituted version of any of these groups;

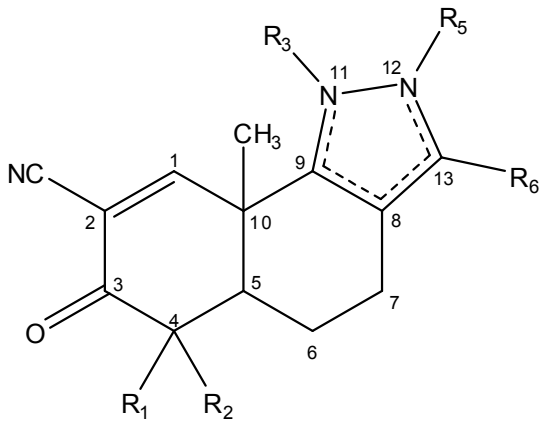
R_3 is absent, hydrogen; or alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$ or a substituted version of any of these groups; provided that R_3 is absent when and only when the atom to which it is bound forms part of a double bond;

R_5 is absent, hydrogen; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups; provided that R_5 is absent when and only when the atom to which it is bound forms part of a double bond; and

R_6 is hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(III),

wherein:

R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq12)}$, $alkenediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups;

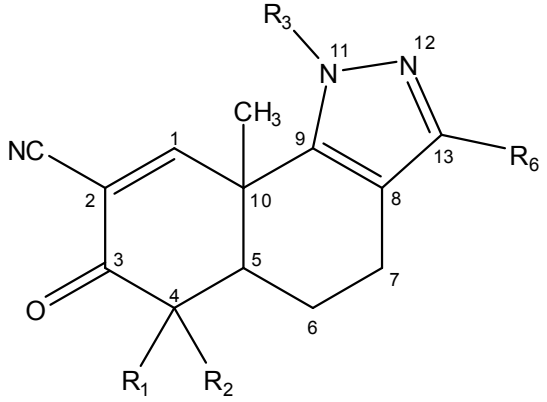
R_3 is absent, hydrogen; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups; provided that R_3 is absent when and only when the atom to which it is bound forms part of a double bond;

R_5 is absent, hydrogen; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups; provided that R_5 is absent when and only when the atom to which it is bound forms part of a double bond; and

R_6 is hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(IV),

wherein:

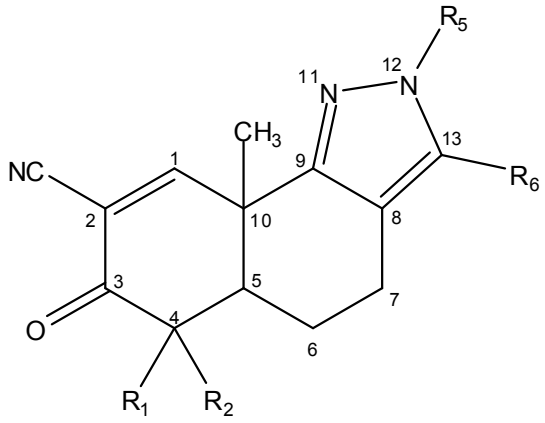
R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

R_3 is hydrogen; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups; and

R_6 is hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(V),

wherein:

R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

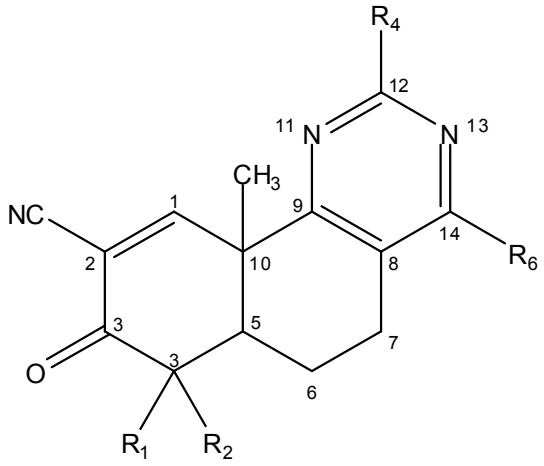
R_1 and R_2 are taken together and are $alkanediyl_{(C\leq12)}$, $alkenediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_5 is hydrogen; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$ or a substituted version of any of these groups; and

R_6 is hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

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



(VI),

wherein:

R_1 and R_2 are each independently hydrogen, hydroxy, halo, or amino; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, hydroxy, amino, halo, or cyano; or $alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$,

arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups;

R_6 is hydrogen, hydroxy, amino, halo, or cyano; or alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups;

or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, the atoms labeled 1 and 2 are connected by a double bond. In some examples, the atoms labeled 1 and 2 are connected by an epoxidized double bond. In some examples, n is 1. In some examples, n is 2. In some examples, m is 0. In some examples, m is 1. In some examples, X is −CN. In some examples, X is $-CF_3$. In some examples, X is hydrogen.

In some examples, R_1 or R_2 is alkyl$_{(C\leq8)}$ or substituted alkyl$_{(C\leq8)}$. In some examples, R_1 or R_2 is alkyl$_{(C\leq8)}$. In some examples, R_1 or R_2 is methyl. In some examples, R_1 and R_2 are each methyl. In some examples, R_1 is methyl and R_2 is hydrogen. In some examples, R_1 or R_2 is ethyl. In some examples, R_1 is ethyl and R_2 is hydrogen. In some examples, R_1 or R_2 is hydrogen. In some examples, R_1 and R_2 are each hydrogen. In some examples, R_1 and R_2 are taken together and are alkanediyl$_{(C\leq8)}$. In some examples, R_1 and R_2 are taken together and are 1,4-butanediyl. In some examples, R_1 or R_2 is aryl$_{(C\leq8)}$. In some examples, R_1 or R_2 is phenyl. In some examples, R_1 is phenyl and R_2 is hydrogen. In some examples, R_1 or R_2 is aralkyl$_{(C\leq8)}$. In some examples, R_1 or R_2 is benzyl. In some examples, R_1 is benzyl and R_2 is hydrogen. In some examples, R_1 and R_2 are each benzyl.

In some examples, R_3 is absent. In some examples, R_3 is hydrogen. In some examples, R_3 is alkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$ or a substituted version of any of these groups. In some examples, R_3 is alkyl$_{(C\leq4)}$ or substituted alkyl$_{(C\leq4)}$. In some examples, R_3 is alkyl$_{(C\leq4)}$. In some examples, R_3 is methyl. In some examples, R_3 is aryl$_{(C\leq8)}$ or substituted aryl$_{(C\leq8)}$. In some examples, R_3 is aryl$_{(C\leq8)}$. In some examples, R_3 is phenyl.

In some examples, R_4 is hydrogen. In some examples, R_4 is oxo. In some examples, R_4 is $alkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or a substituted version of any of these groups. In some examples, R_4 is $alkyl_{(C\leq 6)}$ or substituted $alkyl_{(C\leq 6)}$. In some examples, R_4 is $alkyl_{(C\leq 6)}$. In some examples, R_4 is methyl, isopropyl, *t*-butyl, or cyclopropyl. In some examples, R_4 is $haloalkyl_{(C\leq 6)}$. In some examples, R_4 is trifluoromethyl. In some examples, R_4 is $alkoxy_{(C\leq 6)}$. In some examples, R_4 is methoxy or ethoxy. In some examples, R_4 is $aryl_{(C\leq 8)}$ or substituted $aryl_{(C\leq 8)}$. In some examples, R_4 is phenyl, chlorophenyl, methylphenyl, or methoxyphenyl. In some examples, R_4 is $heteroaryl_{(C\leq 8)}$. In some examples, R_4 is pyridinyl or pyrimidinyl. In some examples, R_4 is $acyl_{(C\leq 6)}$ or substituted $acyl_{(C\leq 6)}$. In some examples, R_4 is ethoxycarbonyl.

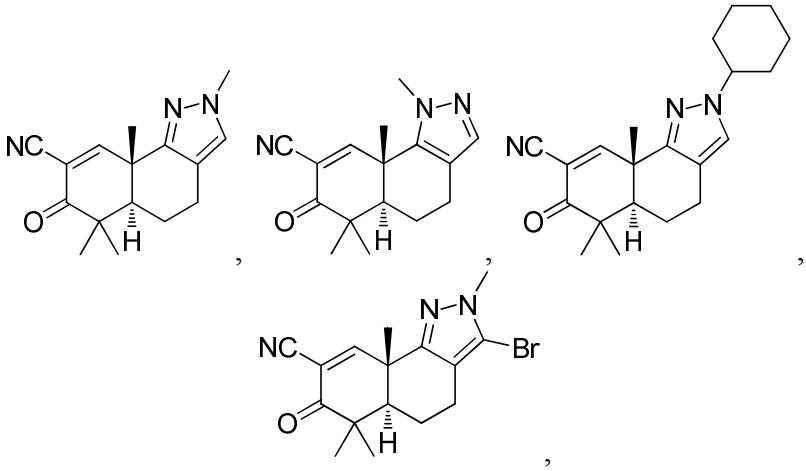
In some examples, R_5 is absent. In some examples, R_5 is hydrogen. In some examples, R_5 is $alkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$ or a substituted version of any of these groups. In some examples, R_5 is $alkyl_{(C\leq 6)}$ or substituted $alkyl_{(C\leq 6)}$. In some examples, R_5 is $alkyl_{(C\leq 6)}$. In some examples, R_5 is methyl, cyclohexyl, or *t*-butyl. In some examples, R_5 is substituted $alkyl_{(C\leq 4)}$. In some examples, R_5 is 2-hydroxyethyl or 2,2,2-trifluoroethyl. In some examples, R_5 is $aryl_{(C\leq 8)}$ or substituted $aryl_{(C\leq 8)}$. In some examples, R_5 is $aryl_{(C\leq 8)}$. In some examples, R_5 is phenyl. In some examples, R_5 is $acyl_{(C\leq 8)}$ or substituted $acyl_{(C\leq 8)}$. In some examples, R_5 is acetyl, methoxycarbonyl, ethoxycarbonyl, or phenylcarbonyl.

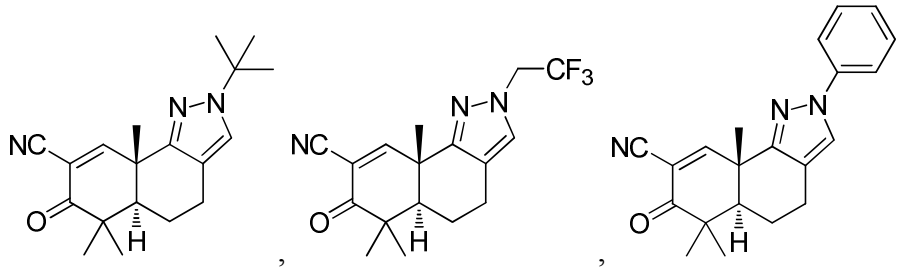
In some examples, R_6 is hydrogen. In some examples, R_6 is cyano. In some examples, R_6 is halo. In some examples, R_6 is chloro or bromo. In some examples, R_6 is $alkyl_{(C\leq 6)}$ or substituted $alkyl_{(C\leq 6)}$. In some examples, R_6 is $alkyl_{(C\leq 6)}$. In some examples, R_6 is methyl, isopropyl or cyclohexyl. In some examples, R_6 is $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$ or a substituted version of either of these groups. In some examples, R_6 is $aryl_{(C\leq 10)}$. In some examples, R_6 is phenyl, methylphenyl or naphthyl. In some examples, R_6 is substituted $aryl_{(C\leq 8)}$. In some examples, R_6 is chlorophenyl, fluorophenyl or methoxyphenyl. In some examples, R_6 is $heteroaryl_{(C\leq 8)}$. In some examples, R_6 is pyridinyl, pyrimidinyl, methylpyrazolyl, dimethylisoxazolyl, methyltriazolyl, or methyltetrazolyl. In some examples, R_6 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$.

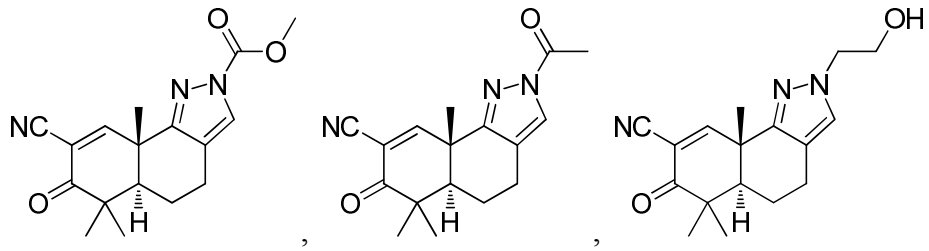
In some examples, R_6 is benzyl. In some examples, R_6 is amido$_{(C\leq 8)}$. In some examples, R_6 is phenylcarbonylamino. In some examples, R_6 is alkynyl$_{(C\leq 8)}$. In some examples, R_6 is ethynyl. In some examples, R_6 is acyl$_{(C\leq 8)}$. In some examples, R_6 is aminocarbonyl or dimethylaminocarbonyl. In some examples, R_6 is alkoxy$_{(C\leq 8)}$. In some examples, R_6 is methoxy. In some examples, carbon atom 10 is in the *R* configuration. In some examples, carbon atom 10 is in the *S* configuration. In some examples, carbon atom 5 is in the *R* configuration. In some examples, carbon atom 5 is in the *S* configuration.

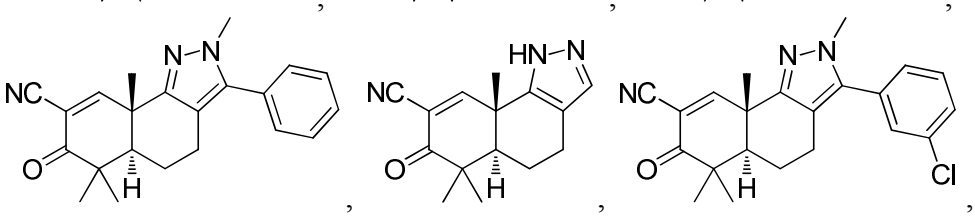
In some examples, R_7 or R_8 is hydrogen. In some examples, R_7 or R_8 is halo. In some examples, R_7 or R_8 is bromo. In some examples, R_7 or R_8 is aryl$_{(C\leq 8)}$. In some examples, R_7 or R_8 is phenyl.

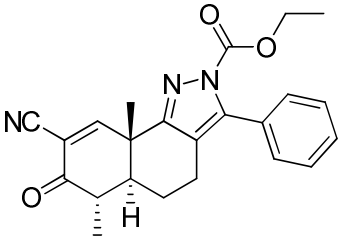
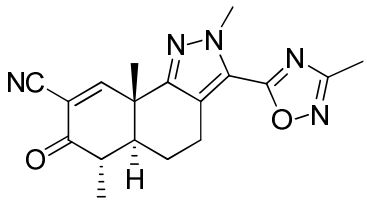
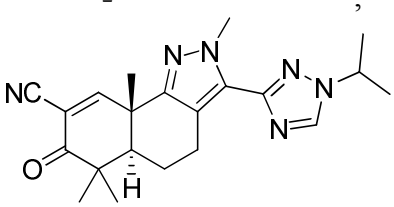
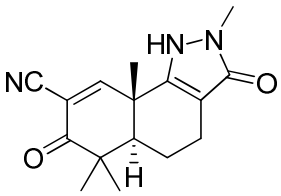
In some examples, the compounds are further defined as:



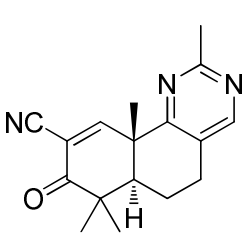
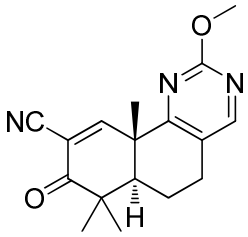
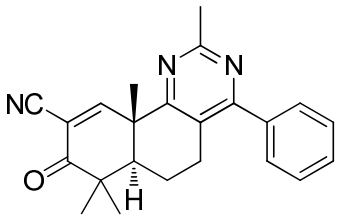




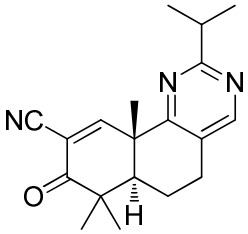
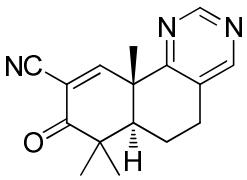
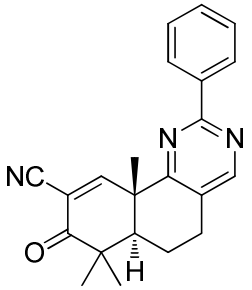


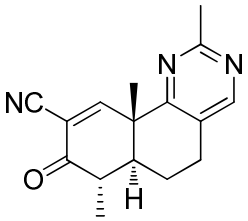
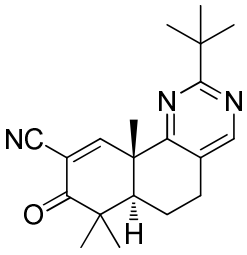
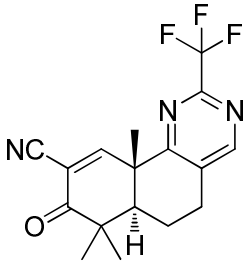

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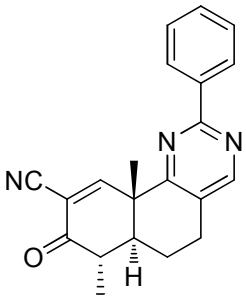
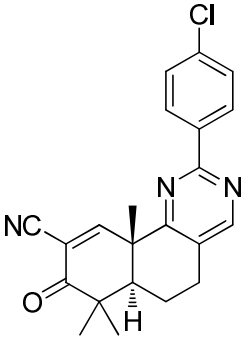
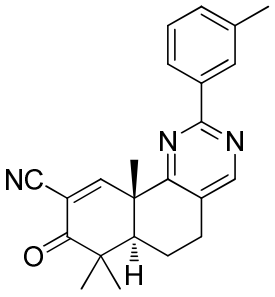
In some examples, the compounds are further defined as:

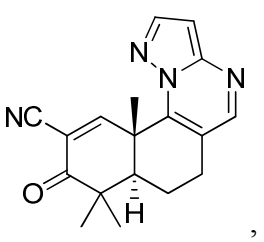
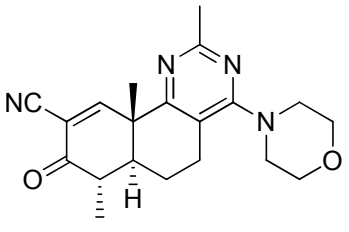
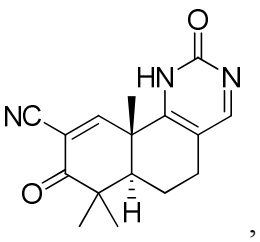
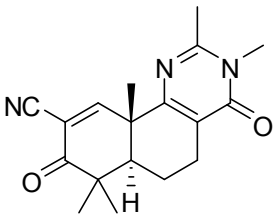
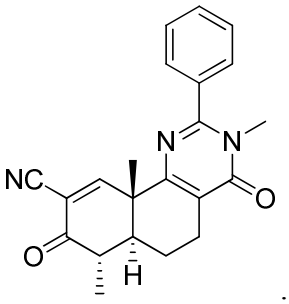

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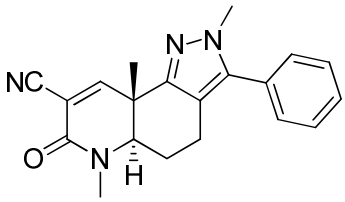
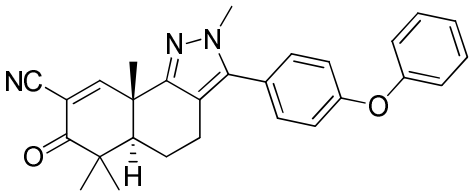
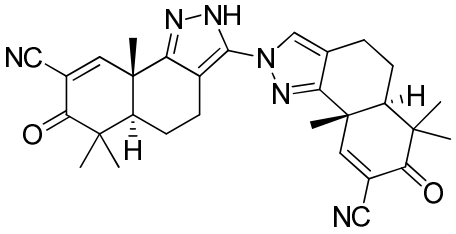
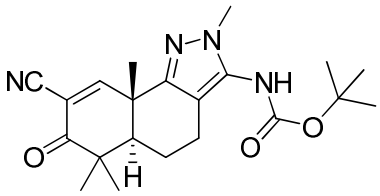
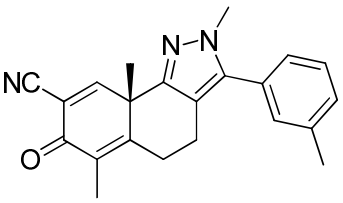
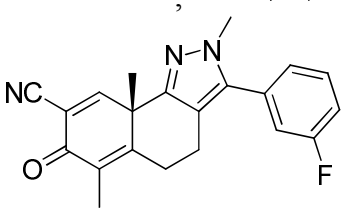
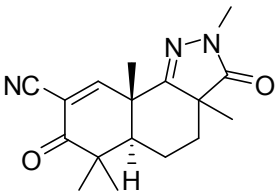
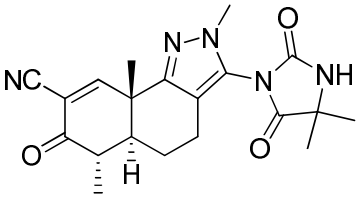
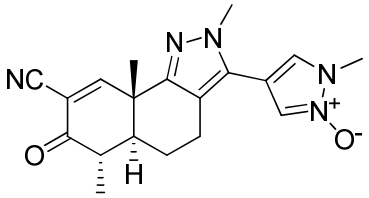

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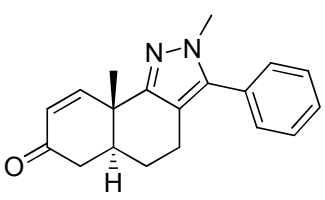
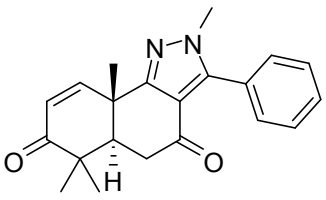
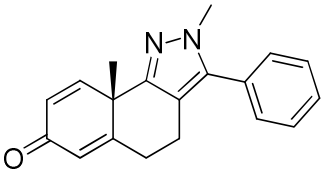

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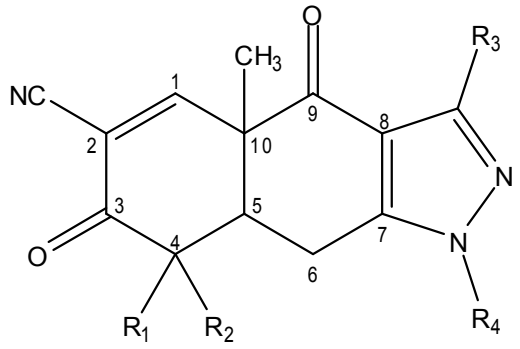
In another example, the disclosure describes compounds of the formulas:


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In another example, the disclosure describes compounds of the formulas:


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In another example, the disclosure describes compounds of the formula:



(VII),

wherein:

R_1 and R_2 are each independently:

hydrogen, hydroxy or amino; or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; or

R_1 and R_2 are taken together and are $alkanediyl_{(C\leq12)}$, $alkenediyl_{(C\leq12)}$, $arenediyl_{(C\leq12)}$, $alkoxydiyl_{(C\leq12)}$, $alkenyloxydiyl_{(C\leq12)}$, $alkylaminodiyl_{(C\leq12)}$, $alkenylaminodiyl_{(C\leq12)}$, or a substituted version of any of these groups;

R_3 is:

hydrogen, hydroxy or amino, or

$alkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $aryloxy_{(C\leq12)}$, $aralkoxy_{(C\leq12)}$, $heteroaryloxy_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $arylamino_{(C\leq12)}$, $aralkylamino_{(C\leq12)}$, $heteroarylamino_{(C\leq12)}$, $amido_{(C\leq12)}$, or a substituted version of any of these groups; and

R_4 is:

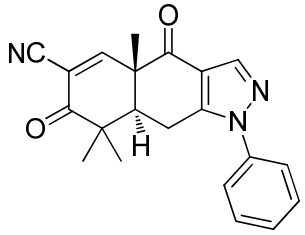
hydrogen; or

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, acyl$_{(C\leq12)}$ or a substituted version of any of these groups;

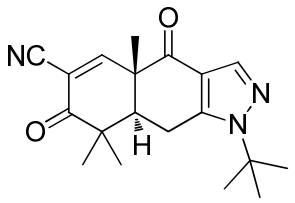
or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, R_1 or R_2 is alkyl$_{(C\leq8)}$ or substituted alkyl$_{(C\leq8)}$. In some examples, R_1 and R_2 are alkyl$_{(C\leq8)}$. In some examples, R_1 and R_2 are methyl. In some examples, R_3 is hydrogen. In some examples, R_4 is aryl$_{(C\leq8)}$ or substituted aryl$_{(C\leq8)}$. In some examples, R_4 is aryl$_{(C\leq8)}$. In some examples, R_4 is phenyl. In some examples, R_4 is alkyl$_{(C\leq6)}$ or substituted alkyl$_{(C\leq6)}$. In some examples, R_4 is alkyl$_{(C\leq6)}$. In some examples, R_4 is *t*-butyl. In some examples, carbon atom 10 is in the *R* configuration. In some examples, carbon atom 10 is in the *S* configuration. In some examples, carbon atom 5 is in the *R* configuration. In some examples, carbon atom 5 is in the *S* configuration.

In some examples, the compounds are further defined as:

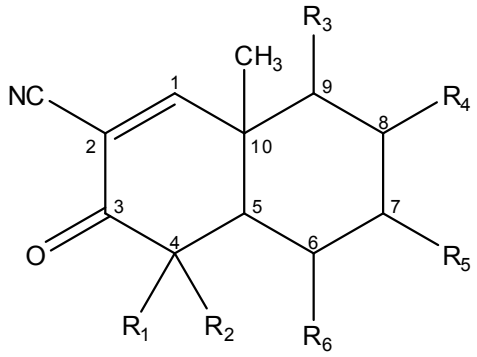


or



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In another example, the disclosure describes compounds of the formula:



(VIII),

wherein:

R_1 and R_2 are each independently:

hydrogen, hydroxy or amino; or

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, aralkoxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$,

alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; or

R_1 and R_2 are taken together and are alkanediyl$_{(C\leq12)}$, alkenediyl$_{(C\leq12)}$, arenediyl$_{(C\leq12)}$, alkoxydiyl$_{(C\leq12)}$, alkenyloxydiyl$_{(C\leq12)}$, alkylaminodiyl$_{(C\leq12)}$, alkenylaminodiyl$_{(C\leq12)}$, or a substituted version of any of these groups; and

R_3, R_4, R_5 and R_6 are each independently:

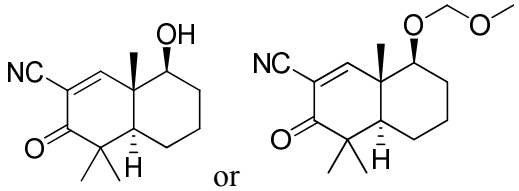
hydrogen, hydroxy or amino, or

alkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heterocycloalkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, alkoxy$_{(C\leq12)}$, aryloxy$_{(C\leq12)}$, heteroaryloxy$_{(C\leq12)}$, acyloxy$_{(C\leq12)}$, alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, arylamino$_{(C\leq12)}$, aralkylamino$_{(C\leq12)}$, heteroarylamino$_{(C\leq12)}$, amido$_{(C\leq12)}$, or a substituted version of any of these groups; and

or a pharmaceutically acceptable salt or tautomer thereof.

In some examples, R_1 or R_2 is alkyl$_{(C\leq8)}$ or substituted alkyl$_{(C\leq8)}$. In some examples, R_1 and R_2 are alkyl$_{(C\leq8)}$. In some examples, R_1 and R_2 are methyl. In some examples, R_4, R_5 and R_6 are hydrogen. In some examples, R_3 is hydroxy. In some examples, R_4 is alkoxy$_{(C\leq6)}$ or substituted alkoxy$_{(C\leq6)}$. In some examples, R_4 is substituted alkoxy$_{(C\leq6)}$. In some examples, R_4 is methoxymethoxy. In some examples, carbon atom 10 is in the *R* configuration. In some examples, carbon atom 10 is in the *S* configuration. In some examples, carbon atom 5 is in the *R* configuration. In some examples, carbon atom 5 is in the *S* configuration.

In some examples, the compounds are further defined as:



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In another example, the disclosure describes pharmaceutical compositions comprising the compound according to any of the formulas disclosed herein and an

excipient. In some examples, the pharmaceutical compositions are further defined as:

a) the compound according to any of the formulas disclosed herein;

b) an optical isomer of the compound, wherein the optical isomer is the enantiomer of the compound; and

c) an excipient.

In some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 1:1. In some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 5:1. In some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 10:1. In some examples, the ratio of the amount of compound to the amount of optical isomer is approximately 20:1.

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.