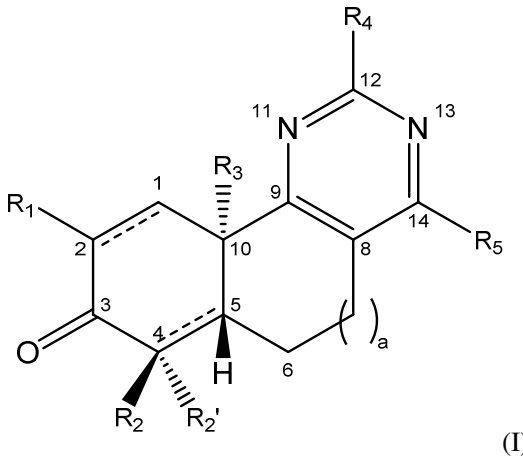
SUMMARY

The present disclosure provides novel compounds, including pyrimidinyl tricyclic enone derivatives with anti-inflammatory and/or antioxidant properties, pharmaceutical compositions thereof, methods for their manufacture, and methods for their use, including for the inhibition of RORγ nuclear receptor the prevention and treatment of diseases or disorders associated with and/or IL-17 overproduction of IL-17.

In one aspect, the present disclosure refers to a compound of the formula:



(I)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

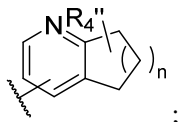
R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of any of these groups, or −alkanediyl$_{(C\leq 8)}$−cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of these groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, or



;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq 12)}$, substituted $arenediyl_{(C\leq 12)}$, $heterocycloalkanediyl_{(C\leq 12)}$, substituted $heterocycloalkanediyl_{(C\leq 12)}$, $heteroarenediyl_{(C\leq 12)}$, or substituted $heteroarenediyl_{(C\leq 12)}$;

p is 0, 1, 2, 3, or 4; and

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, isopropoxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, or a substituted version of any of the last thirteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

$$-Y_2-C(O)NR_c-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq 8)}$ or substituted $arenediyl_{(C\leq 8)}$;

R_c is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

A_2 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$; or

$$-A_3R_d$$;

wherein:

A_3 is −O− or $-NR_e-$, wherein

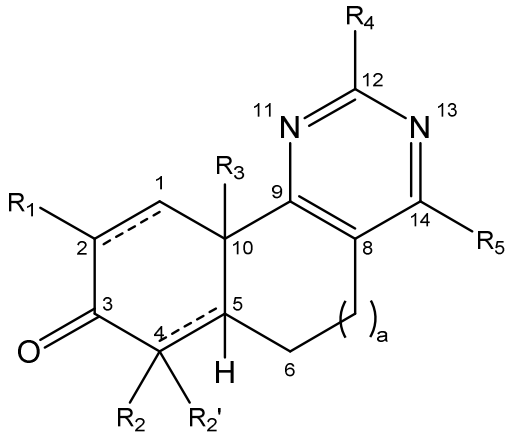
R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure refers to a compound of the formula:



(X)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

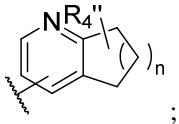
R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, or −alkanediyl$_{(C\leq 8)}$−cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, or



;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, −C(O)−alkoxy$_{(C\leq 8)}$, −C(O)−alkylamino$_{(C\leq 8)}$, −C(O)−dialkyl-amino$_{(C\leq 8)}$, alkylsulfonyl$_{(C\leq 8)}$, arylsulfonyl$_{(C\leq 8)}$, alkoxysulfonyl$_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is arenediyl$_{(C\leq12)}$, substituted arenediyl$_{(C\leq12)}$, heterocycloalkyldiyl$_{(C\leq12)}$, substituted heterocycloalkyldiyl$_{(C\leq12)}$, heteroarenediyl$_{(C\leq12)}$, or substituted heteroarenediyl$_{(C\leq12)}$;

p is 0, 1, 2, 3, or 4; and

$R_4‴$ is alkyl$_{(C\leq8)}$, cycloalkyl$_{(C\leq8)}$, aryl$_{(C\leq8)}$, heteroaryl$_{(C\leq8)}$, heterocycloalkyl$_{(C\leq8)}$, acyl$_{(C\leq8)}$, alkoxy$_{(C\leq8)}$, acyloxy$_{(C\leq8)}$, −C(O)−alkoxy$_{(C\leq8)}$, −C(O)−alkylamino$_{(C\leq8)}$, −C(O)−dialkyl-amino$_{(C\leq8)}$, alkylsulfonyl$_{(C\leq8)}$, arylsulfonyl$_{(C\leq8)}$, alkoxysulfonyl$_{(C\leq8)}$, or a substituted version of any of these groups; and

R_5 is cycloalkoxy$_{(C\leq12)}$, aryl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, or a substituted version of any of the last three groups, or

$$-OY_1-A_1;$$

wherein:

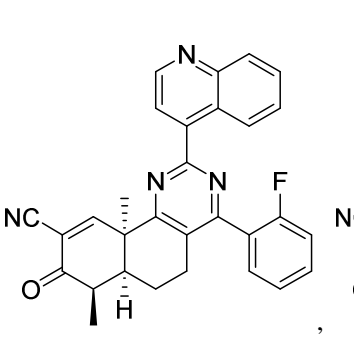
Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$; or

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure refers to a compound of the formula: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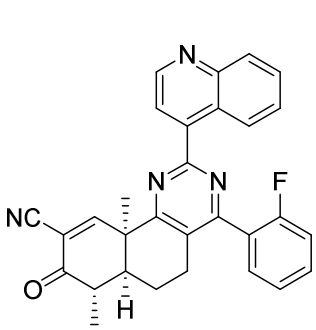
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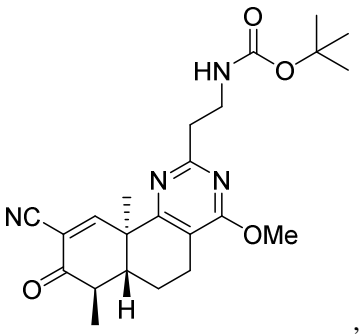
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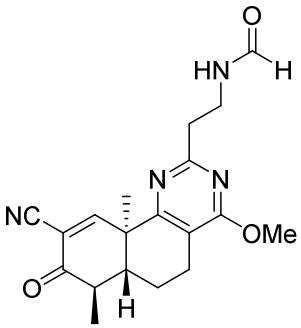
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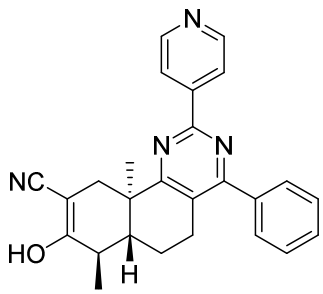
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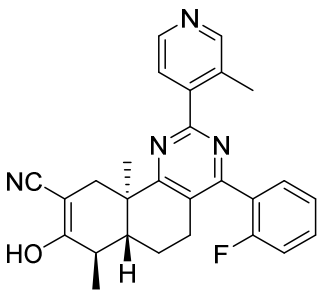
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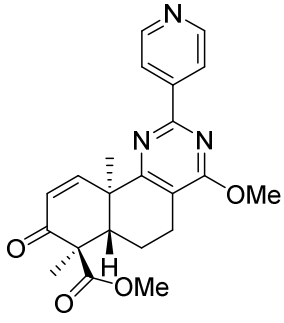

;

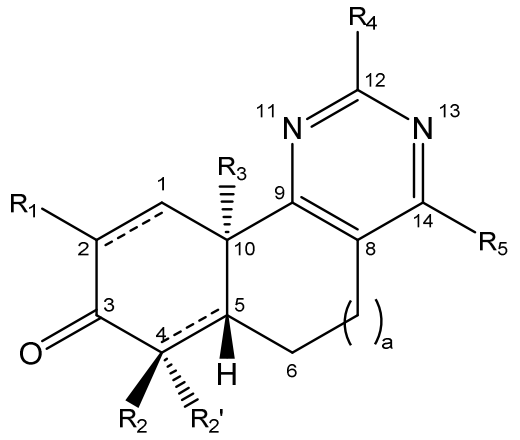
or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising: (A) a compound as disclosed herein; and (B) an excipient; optionally the pharmaceutical composition is formulated for oral administration, administration via injection such as intraarterial administration, intramuscular administration, intraperitoneal administration, or intravenous administration, or topical administration such as topical administration to the skin or to the eye

In yet another aspect, the present disclosure refers to a compound or composition as disclosed herein for use as a medicament.

In yet another aspect, the present disclosure refers to use of a compound or composition as disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder selected from autoimmune disease, organ rejection, asthma, cancer, a neurological disease, a psychiatric disorder, a neuropsychiatric disorder, chronic pain syndrome, an inflammatory condition, a retinal disorder, or a cardiovascular diseases in a patient in need thereof.

In some examples, the present disclosure provides compounds of the formula:



(I)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of these groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

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

R_4 is hydrogen, amino, $alkyl_{(C\leq18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted

$-Y_2-C(O)NR_c-A_2$;

wherein:

Y_2 is arenediyl$_{(C\leq 8)}$ or substituted arenediyl$_{(C\leq 8)}$;

R_c is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

A_2 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$; or

$-A_3R_d$;

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

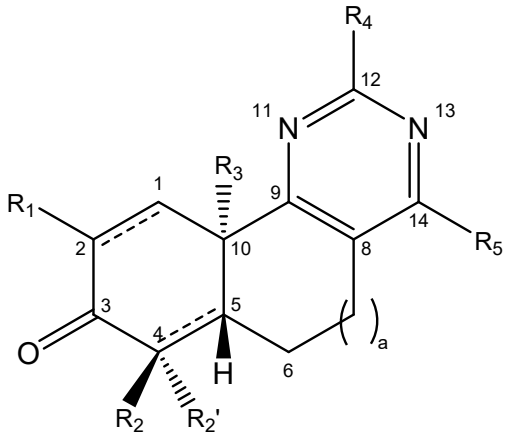
R_e is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

R_d is acyl$_{(C\leq 12)}$, or substituted acyl$_{(C\leq 12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some examples, the present disclosure provides compounds of the formula:



(I)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of these

alkylamino$_{(C\leq12)}$, dialkylamino$_{(C\leq12)}$, alkylsulfonylamino$_{(C\leq12)}$, or a substituted version of any of the last eleven groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is alkanediyl$_{(C\leq8)}$ or substituted alkanediyl$_{(C\leq8)}$; and

A_1 is cycloalkyl$_{(C\leq8)}$ or substituted cycloalkyl$_{(C\leq8)}$; or

$$-Y_2-C(O)NR_c-A_2;$$

wherein:

Y_2 is arenediyl$_{(C\leq8)}$ or substituted arenediyl$_{(C\leq8)}$;

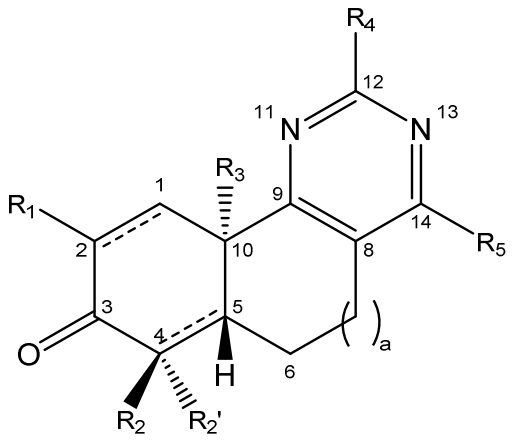
R_c is hydrogen, alkyl$_{(C\leq6)}$, or substituted alkyl$_{(C\leq6)}$; and

A_2 is aralkyl$_{(C\leq12)}$ or substituted aralkyl$_{(C\leq12)}$; or

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some examples, the compounds are further defined as:



(I)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq8)}$, substituted heteroaryl$_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq8)}$, alkylamino$_{(C\leq8)}$, dialkylamino$_{(C\leq8)}$, alkylsulfonylamino$_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq8)}-$cycloalkyl$_{(C\leq12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq12)}$, cycloalkyl$_{(C\leq12)}$, alkenyl$_{(C\leq12)}$, alkynyl$_{(C\leq12)}$, aryl$_{(C\leq12)}$, aralkyl$_{(C\leq12)}$, heteroaryl$_{(C\leq12)}$, heteroaralkyl$_{(C\leq12)}$, acyl$_{(C\leq12)}$, or a substituted version of these

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq12)}$, $alkoxy_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $cycloalkoxy_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $heterocycloalkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, $acyloxy_{(C\leq12)}$, $alkylamino_{(C\leq12)}$, $dialkylamino_{(C\leq12)}$, $alkylsulfonylamino_{(C\leq12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is $alkanediyl_{(C\leq8)}$ or substituted $alkanediyl_{(C\leq8)}$; and

A_1 is $cycloalkyl_{(C\leq8)}$ or substituted $cycloalkyl_{(C\leq8)}$; or

$$-Y_2-C(O)NR_c-A_2;$$

wherein:

Y_2 is $arenediyl_{(C\leq8)}$ or substituted $arenediyl_{(C\leq8)}$;

R_c is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

A_2 is $aralkyl_{(C\leq12)}$ or substituted $aralkyl_{(C\leq12)}$; or

$$-A_3R_d;$$

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

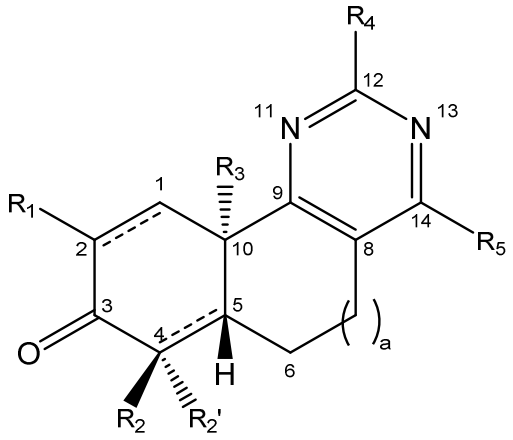
R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In other examples, the compounds are further defined as:



(I)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

p is 0, 1, 2, 3, or 4; and

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq 12)}$, $alkoxy_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, or a substituted version of any of the last fourteen groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

$$-Y_2-C(O)NR_c-A_2;$$

wherein:

Y_2 is $arenediyl_{(C\leq 8)}$ or substituted $arenediyl_{(C\leq 8)}$;

R_c is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

A_2 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$; or

$$-A_3R_d;$$

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

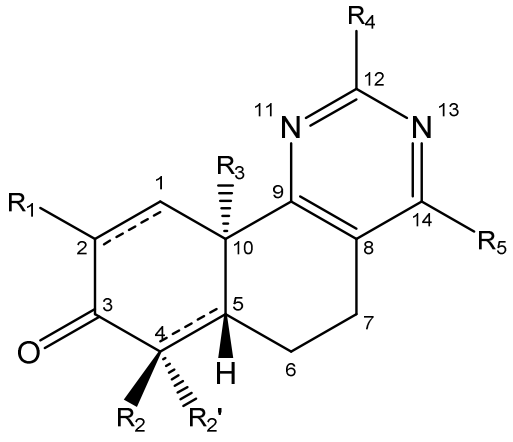
R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

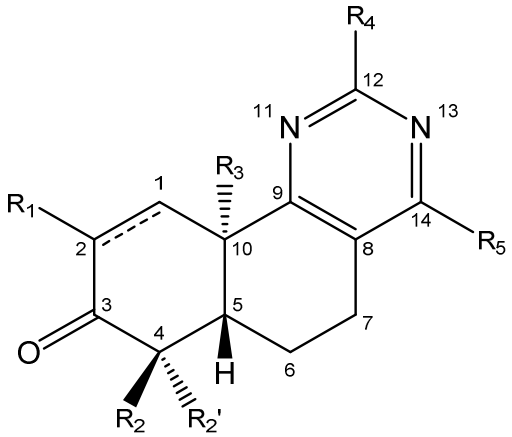
In some examples, the compounds are further defined as:



(II)

wherein:

In some examples, the compounds are further defined as:



(III)

wherein:

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

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of any of these groups, or $-$alkanediyl$_{(C\leq 8)}-$cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups;

R_3 is alkyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, alkyl$_{(C2\text{-}18)}$, substituted alkyl$_{(C\leq 18)}$, cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, substituted aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, substituted heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, alkylamino$_{(C\leq 18)}$, substituted alkylamino$_{(C\leq 18)}$, dialkylamino$_{(C\leq 18)}$, substituted dialkylamino$_{(C\leq 18)}$, alkylthio$_{(C\leq 18)}$, substituted alkylthio$_{(C\leq 18)}$, amido$_{(C\leq 18)}$, substituted amido$_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

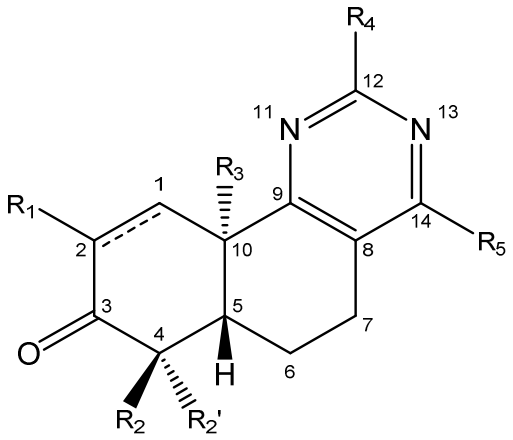
m is 0, 1, 2, 3, or 4; and

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In other examples, the compounds are further defined as:



(III)

wherein:

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

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_2' is hydrogen, $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, or a substituted version of the last four groups;

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

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

m is 0, 1, 2, 3, or 4; and

wherein:

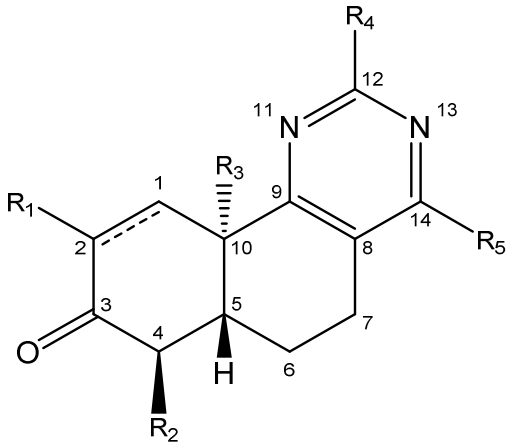
A_3 is −O− or −NR_e−, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some examples, the compounds are further defined as:



(IV)

wherein:

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

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, −CF_3, or –C(O)R_a; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or −$alkanediyl_{(C\leq8)}$−$cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

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

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

m is 0, 1, 2, 3, or 4; and

wherein:

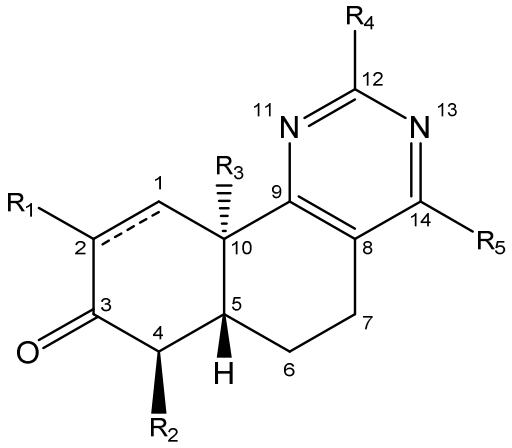
A_3 is −O− or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

In other examples, the compounds are further defined as:



(IV)

wherein:

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

R_1 is cyano, $heteroaryl_{(C\leq 8)}$, substituted $heteroaryl_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq 8)}-cycloalkyl_{(C\leq 12)}$ or a substituted version of this group;

R_3 is $alkyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq 18)}$, substituted $cycloalkyl_{(C\leq 18)}$, $aryl_{(C\leq 18)}$, substituted $aryl_{(C\leq 18)}$, $aralkyl_{(C\leq 18)}$, substituted $aralkyl_{(C\leq 18)}$, $heteroaryl_{(C\leq 18)}$, substituted $heteroaryl_{(C\leq 18)}$, $heteroaralkyl_{(C\leq 18)}$, substituted $heteroaralkyl_{(C\leq 18)}$, $heterocycloalkyl_{(C\leq 18)}$, substituted $heterocycloalkyl_{(C\leq 18)}$, $alkylamino_{(C\leq 18)}$, substituted $alkylamino_{(C\leq 18)}$, $dialkylamino_{(C\leq 18)}$, substituted $dialkylamino_{(C\leq 18)}$, $alkylthio_{(C\leq 18)}$, substituted $alkylthio_{(C\leq 18)}$, $amido_{(C\leq 18)}$, substituted $amido_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$;

m is 0, 1, 2, 3, or 4; and

wherein:

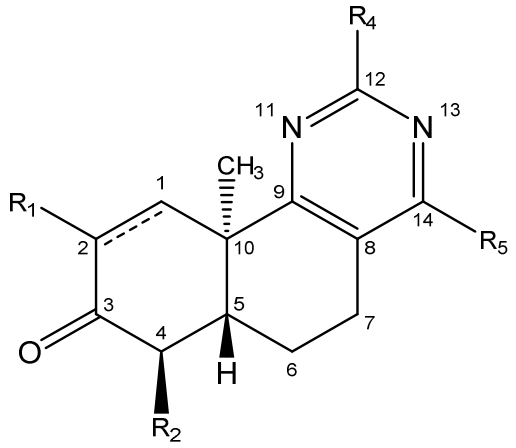
A_3 is −O− or −NR_e−, wherein

R_e is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$; and

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some examples, the compounds are further defined as:



(V)

wherein:

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

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $–CF_3$, or $–C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or −$alkanediyl_{(C\leq8)}$−$cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$–X_1–(CH_2)_m–R_4';$$

wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

m is 0, 1, 2, 3, or 4; and

wherein:

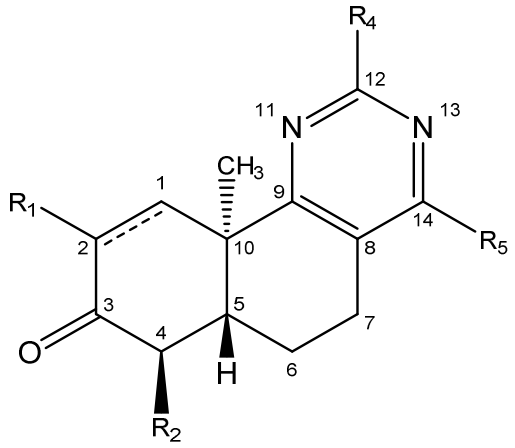
A_3 is −O− or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

In other examples, the compounds are further defined as:



(V)

wherein:

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

R_1 is cyano, $heteroaryl_{(C\leq 8)}$, substituted $heteroaryl_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq 8)}-cycloalkyl_{(C\leq 12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq 18)}$, substituted $cycloalkyl_{(C\leq 18)}$, $aryl_{(C\leq 18)}$, substituted $aryl_{(C\leq 18)}$, $aralkyl_{(C\leq 18)}$, substituted $aralkyl_{(C\leq 18)}$, $heteroaryl_{(C\leq 18)}$, substituted $heteroaryl_{(C\leq 18)}$, $heteroaralkyl_{(C\leq 18)}$, substituted $heteroaralkyl_{(C\leq 18)}$, $heterocycloalkyl_{(C\leq 18)}$, substituted $heterocycloalkyl_{(C\leq 18)}$, $alkylamino_{(C\leq 18)}$, substituted $alkylamino_{(C\leq 18)}$, $dialkylamino_{(C\leq 18)}$, substituted $dialkylamino_{(C\leq 18)}$, $alkylthio_{(C\leq 18)}$, substituted $alkylthio_{(C\leq 18)}$, $amido_{(C\leq 18)}$, substituted $amido_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$;

m is 0, 1, 2, 3, or 4; and

wherein:

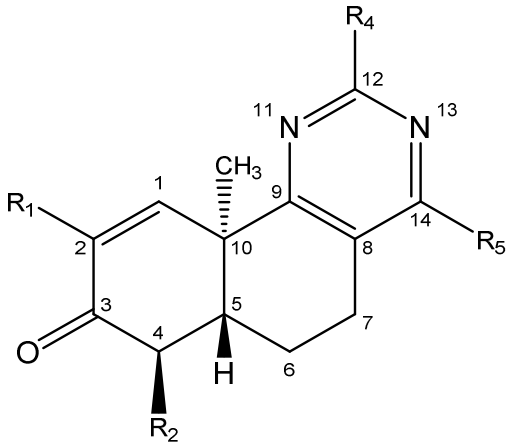
A_3 is −O− or $-NR_e-$, wherein

R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

In some examples, the compounds are further defined as:



(VI)

wherein:

R_1 is cyano, $heteroaryl_{(C\leq 8)}$, substituted $heteroaryl_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $alkylsulfonylamino_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $alkenyl_{(C\leq 12)}$, $alkynyl_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq 8)}-cycloalkyl_{(C\leq 12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq 18)}$, $cycloalkyl_{(C\leq 18)}$, substituted $cycloalkyl_{(C\leq 18)}$, $aryl_{(C\leq 18)}$, substituted $aryl_{(C\leq 18)}$, $aralkyl_{(C\leq 18)}$, substituted $aralkyl_{(C\leq 18)}$, $heteroaryl_{(C\leq 18)}$, substituted $heteroaryl_{(C\leq 18)}$, $heteroaralkyl_{(C\leq 18)}$, substituted $heteroaralkyl_{(C\leq 18)}$, $heterocycloalkyl_{(C\leq 18)}$, substituted $heterocycloalkyl_{(C\leq 18)}$, $alkylamino_{(C\leq 18)}$, substituted $alkylamino_{(C\leq 18)}$, $dialkylamino_{(C\leq 18)}$, substituted $dialkylamino_{(C\leq 18)}$, $alkylthio_{(C\leq 18)}$, substituted $alkylthio_{(C\leq 18)}$, $amido_{(C\leq 18)}$, substituted $amido_{(C\leq 18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$;

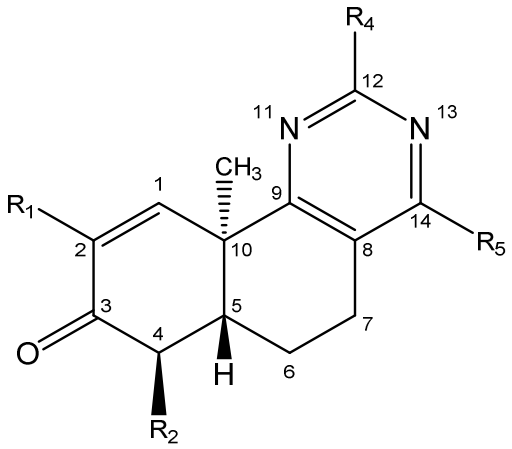
m is 0, 1, 2, 3, or 4; and

R_4' is $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 18)}$, $aryl_{(C\leq 18)}$, $aralkyl_{(C\leq 18)}$, $heteroaryl_{(C\leq 18)}$, $heteroaralkyl_{(C\leq 18)}$, $heterocycloalkyl_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or

R_d is $acyl_{(C\leq12)}$, or substituted $acyl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In other examples, the compounds are further defined as:



(VI)

wherein:

R_1 is cyano, $heteroaryl_{(C\leq8)}$, substituted $heteroaryl_{(C\leq8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or $alkoxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $alkylsulfonylamino_{(C\leq8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

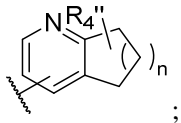
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

m is 0, 1, 2, 3, or 4; and

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or

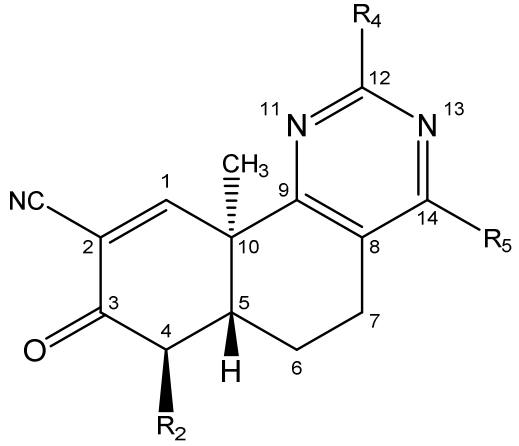


;

wherein:

n is 0, 1, 2, 3, or 4; and

In some examples, the compounds are further defined as:



(VII)

wherein:

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $alkyl_{(C2\text{-}18)}$, substituted $alkyl_{(C\leq18)}$, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

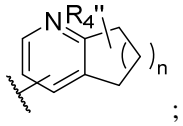
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

m is 0, 1, 2, 3, or 4; and

R_4' is $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl; or



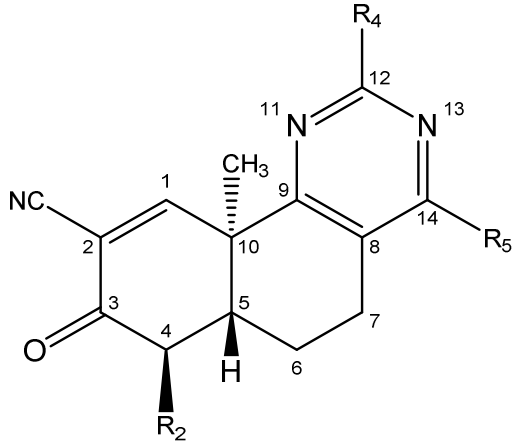
;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$,

In other examples, the compounds are further defined as:



(VII)

wherein:

R_2 is hydrogen or $alkyl_{(C\leq12)}$, $cycloalkyl_{(C\leq12)}$, $alkenyl_{(C\leq12)}$, $alkynyl_{(C\leq12)}$, $aryl_{(C\leq12)}$, $aralkyl_{(C\leq12)}$, $heteroaryl_{(C\leq12)}$, $heteroaralkyl_{(C\leq12)}$, $acyl_{(C\leq12)}$, or a substituted version of any of these groups, or $-alkanediyl_{(C\leq8)}-cycloalkyl_{(C\leq12)}$ or a substituted version of this group;

R_4 is hydrogen, amino, $cycloalkyl_{(C\leq18)}$, substituted $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, substituted $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, substituted $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, substituted $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, substituted $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, substituted $heterocycloalkyl_{(C\leq18)}$, $alkylamino_{(C\leq18)}$, substituted $alkylamino_{(C\leq18)}$, $dialkylamino_{(C\leq18)}$, substituted $dialkylamino_{(C\leq18)}$, $alkylthio_{(C\leq18)}$, substituted $alkylthio_{(C\leq18)}$, $amido_{(C\leq18)}$, substituted $amido_{(C\leq18)}$, or

$$-X_1-(CH_2)_m-R_4';$$

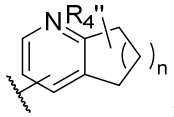
wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, $alkyl_{(C\leq6)}$, or substituted $alkyl_{(C\leq6)}$;

m is 0, 1, 2, 3, or 4; and

R_4' is $cycloalkyl_{(C\leq18)}$, $aryl_{(C\leq18)}$, $aralkyl_{(C\leq18)}$, $heteroaryl_{(C\leq18)}$, $heteroaralkyl_{(C\leq18)}$, $heterocycloalkyl_{(C\leq18)}$, or a substituted version of any of these groups; or



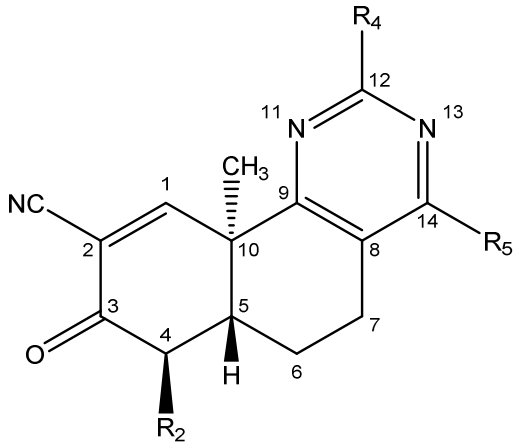
;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is $-H$, $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CN$, $-SH$, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$,

In some examples, the compounds are further defined as:



(VII)

wherein:

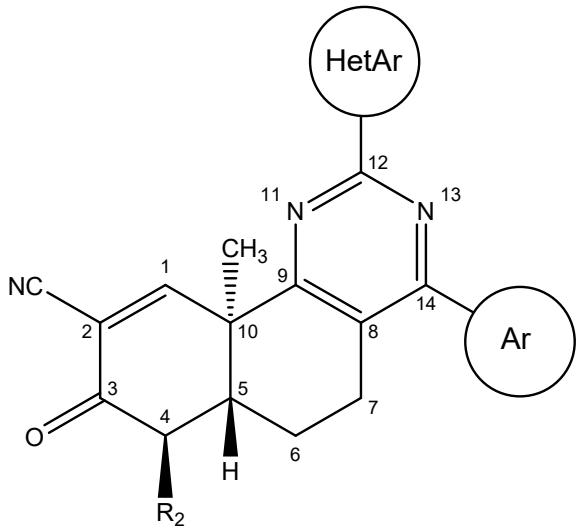
R_2 is hydrogen, $alkyl_{(C\leq12)}$, or $substituted\ alkyl_{(C\leq12)}$;

R_4 is $heteroaryl_{(C\leq18)}$ or $substituted\ heteroaryl_{(C\leq18)}$; and

R_5 is $aryl_{(C\leq12)}$ or $substituted\ aryl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some examples, the compounds are further defined as:



(VIII)

wherein:

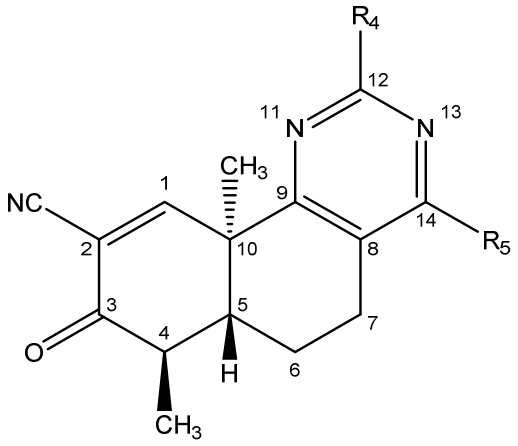
R_2 is $alkyl_{(C\leq12)}$ or $substituted\ alkyl_{(C\leq12)}$;

HetAr is $heteroaryl_{(C\leq18)}$ or $substituted\ heteroaryl_{(C\leq18)}$; and

Ar is $aryl_{(C\leq12)}$ or $substituted\ aryl_{(C\leq12)}$;

or a pharmaceutically acceptable salt thereof.

In some examples, the compounds are further defined as:



(IX)

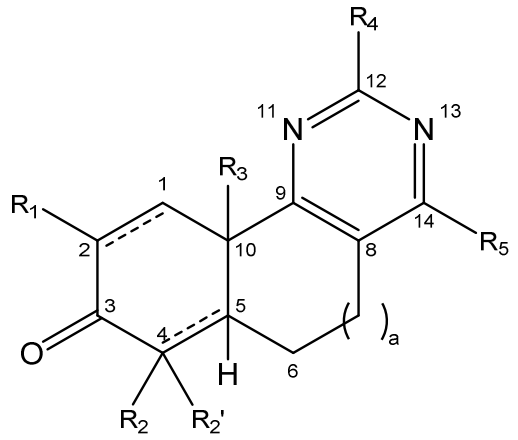
wherein:

R_4 is heteroaryl$_{(C\leq 18)}$ or substituted heteroaryl$_{(C\leq 18)}$; and

R_5 is aryl$_{(C\leq 12)}$ or substituted aryl$_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

In other examples, the present disclosure provides compounds of the formula:



(X)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, or −alkanediyl$_{(C\leq 8)}$−cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$; or

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

In some examples, the bond between carbon atom 1 and carbon atom 2 is an epoxidized double bond. In other examples, the bond between carbon atom 1 and carbon atom 2 is a double bond. In some examples, the bond between carbon atom 4 and carbon atom 5 is a single bond. In other examples, the bond between carbon atom 4 and carbon atom 5 is a double bond. In some examples, a is 1. In some examples, R_1 is cyano.

In some examples, R_2 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$. In some examples, R_2 is alkyl$_{(C\leq 12)}$ such as methyl, ethyl, or propyl. In some examples, R_2 is methyl. In some examples, R_2 is substituted alkyl$_{(C\leq 12)}$ such as 3-hydroxypropyl. In other examples, R_2 is alkenyl$_{(C\leq 12)}$ or substituted alkenyl$_{(C\leq 12)}$. In some examples, R_2 is alkenyl$_{(C\leq 12)}$ such as 2-propenyl. In some examples, R_2' is hydrogen. In other examples, R_2' is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$. In some examples, R_2' is alkyl$_{(C\leq 12)}$ such as methyl.

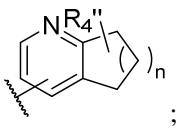
In some examples, R_3 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$. In some examples, R_3 is alkyl$_{(C\leq 12)}$ such as methyl, propyl, or isopentyl. In some examples, R_3 is methyl. In other examples, R_3 is aryl$_{(C\leq 12)}$ or substituted aryl$_{(C\leq 12)}$. In some examples, R_3 is aryl$_{(C\leq 12)}$ such as phenyl.

In some examples, R_4 is alkyl$_{(C2\text{-}18)}$ or substituted alkyl$_{(C2\text{-}18)}$. In other examples, R_4 is heteroaryl$_{(C\leq 18)}$ or substituted heteroaryl$_{(C\leq 18)}$. In some examples, R_4 is a heteroaryl$_{(C\leq 12)}$ or a substituted heteroaryl$_{(C\leq 12)}$ group wherein at least one of the heteroatoms in the aromatic ring is a nitrogen atom. In some examples, R_4 is heteroaryl$_{(C\leq 18)}$ such as 3-pyridinyl, 4-pyridinyl, 4-(2-cycylopropyl)-pyridinyl, 5-(2-cycylopropyl)-pyridinyl, 4-(2-morpholino)-pyridinyl, 4-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 3-(6-methyl)-pyridinyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-pyrazolo[1,5-*a*]pyridinyl, 3-(*N*-methyl)-pyrrolo[2,3-*b*]pyridinyl, 5-isoquinlinyl, 2-isoquinlinyl, 1-isoquinolinyl, 4-(2-phenyl)-pyridinyl, 5-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 4-(3,5-dimethyl)-isoxazolyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-(4-methyl)-pyridinyl, 4-(6-methyl)-pyrimidinyl, 6-(4-methyl)-pyrimidinyl, 4-pyridazinyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 5-quinolinyl, 6-quinolinyl, 8-quinolinyl, 4-isoquinolinyl, 3-(8-methyl)-quinolinyl, 3-(1-methyl)-quinolinyl, 4-(2-methyl)-quinolinyl, 4-(2-isopropyl)-quinolinyl, 4-(6-methyl)-quinolinyl, 4-(7-methyl)-quinolinyl, 4-(8-methyl)-quinolinyl, 2-(*N*-methyl)-indolyl, 5-(2,4-dimethyl)-thiazolyl, or 5-(3-methyl)-oxadizolyl. In other examples, R_4 is substituted heteroaryl$_{(C\leq 18)}$ such as 4-(2-trifluoromethyl)-pyridinyl, 4-(3-fluoro)-pyridinyl, 4-(2-methoxy)-pyridinyl, 4-(2-hydroxymethyl)-pyridinyl, 4-(2-acetylamino)-pyridinyl, 4-(2-fluoromethyl)-pyridinyl, 4-(2-acetamidylethyl)-pyridinyl, 4-(2-fluoromethyl)-quinolinyl, 4-(2-acetoxymethyl)-quinolinyl, 4-(2-formyl)-

quinolinyl, 4-(6-fluoro)-quinolinyl, 4-(7-fluoro)-quinolinyl, 4-(8-fluoro)-quinolinyl, 4-(6,8-difluoro)-quinolinyl, 4-(6-fluoro-2-methyl)-quinolinyl, or 4-(8-fluoro-2-methyl)-quinolinyl.

In other examples, R_4 is $aryl_{(C\leq12)}$ or substituted $aryl_{(C\leq12)}$. In some examples, R_4 is $aryl_{(C\leq12)}$ such as phenyl. In other examples, R_4 is substituted $aryl_{(C\leq12)}$ such as 2-fluorophenyl or 4-trifluoromethylphenyl. In other examples, R_4 is $cycloalkyl_{(C\leq12)}$ or substituted $cycloalkyl_{(C\leq12)}$. In some examples, R_4 is $cycloalkyl_{(C\leq12)}$ such as cyclohexyl.

In other examples, R_4 is:



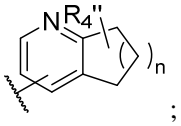
;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups.

In other examples, R_4 is:



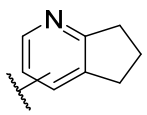
;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq8)}$, $cycloalkyl_{(C\leq8)}$, $aryl_{(C\leq8)}$, $heteroaryl_{(C\leq8)}$, $heterocycloalkyl_{(C\leq8)}$, $acyl_{(C\leq8)}$, $amido_{(C\leq8)}$, $alkoxy_{(C\leq8)}$, $acyloxy_{(C\leq8)}$, $alkylamino_{(C\leq8)}$, $dialkylamino_{(C\leq8)}$, $-C(O)-alkoxy_{(C\leq8)}$, $-C(O)-alkylamino_{(C\leq8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq8)}$, $alkylsulfonyl_{(C\leq8)}$, $arylsulfonyl_{(C\leq8)}$, $alkoxysulfonyl_{(C\leq8)}$, or a substituted version of any of these groups.

In some examples, R_4 is:



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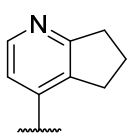
In some examples, R_4 is:



.

In other examples, R_4 is heterocycloalkyl$_{(C\leq 18)}$ or substituted heterocycloalkyl$_{(C\leq 18)}$. In some examples, R_4 is heterocycloalkyl$_{(C\leq 12)}$ such as morpholinyl, 4-piperidinyl, 3-(5-methyl-)1,2,3,6-tetrahydropyridinyl, or 4-*N*-methylpiperazinyl. In other examples, R_4 is substituted heterocycloalkyl$_{(C\leq 12)}$ such as *N*-*t*-butyloxycarbonyl-4-piperidinyl, *N*-acetyl-4-piperidinyl, *N*-*t*-butyloxycarbonyl-5-methyl-1,2,3,6-tetrahydropyridinyl, *N*-acetyl-5-methyl-1,2,3,6-tetrahydropyridinyl, or 4-*N*-acetylpiperazinyl. In other examples, R_4 is hydrogen.

In other examples, R_4 is $-X_1-(CH_2)_m-R_4'$; wherein:

X_1 is NR_b, O, or S; wherein:

R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

m is 0, 1, 2, 3, or 4; and

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups, provided that when X_1 is O, then R_4' is not methyl.

In other examples, R_4 is $-X_1-(CH_2)_m-R_4'$; wherein:

X_1 is NR_b, O, or S; wherein:

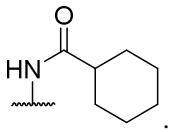
R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$;

m is 0, 1, 2, 3, or 4; and

R_4' is alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups.

In some examples, X_1 is NR_b, wherein: R_b is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$. In some examples, R_b is hydrogen. In some examples, m is 0 or 1. In some examples, m is 0. In some examples, R_4' is cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, aralkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, heteroaralkyl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, or a substituted version of any of these groups. In some examples, R_4' is heteroaryl$_{(C\leq 12)}$ or substituted heteroaryl$_{(C\leq 12)}$. In some examples, R_4' is heteroaryl$_{(C\leq 12)}$ such as 4-pyridinyl.

In other examples, R_4 is amino. In other examples, R_4 is amido$_{(C\leq 12)}$ or substituted amido$_{(C\leq 12)}$. In some examples, R_4 is amido$_{(C\leq 12)}$ such as:



In other example, R_4 is $-X_2-(CH_2)_p-R_4'''$; wherein:

X_2 is arenediyl$_{(C\leq 12)}$, substituted arenediyl$_{(C\leq 12)}$, heterocycloalkanediyl$_{(C\leq 12)}$, substituted heterocycloalkanediyl$_{(C\leq 12)}$, heteroarenediyl$_{(C\leq 12)}$, or substituted heteroarenediyl$_{(C\leq 12)}$;

p is 0, 1, 2, 3, or 4; and

R_4''' is alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, $-C(O)-$alkoxy$_{(C\leq 8)}$, $-C(O)-$alkylamino$_{(C\leq 8)}$,

−C(O)−dialkylamino$_{(C\leq 8)}$, alkylsulfonyl$_{(C\leq 8)}$, arylsulfonyl$_{(C\leq 8)}$, alkoxysulfonyl$_{(C\leq 8)}$, or a substituted version of any of these groups.

In other examples, $-X_2-(CH_2)_p-R_4'''$; wherein:

X_2 is heterocycloalkanediyl$_{(C\leq 12)}$, substituted heterocycloalkanediyl$_{(C\leq 12)}$, heteroarenediyl$_{(C\leq 12)}$, or substituted heteroarenediyl$_{(C\leq 12)}$;

p is 0, 1, 2, 3, or 4; and

R_4''' is alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, −C(O)−alkoxy$_{(C\leq 8)}$, −C(O)−alkylamino$_{(C\leq 8)}$, −C(O)−dialkylamino$_{(C\leq 8)}$, alkylsulfonyl$_{(C\leq 8)}$, arylsulfonyl$_{(C\leq 8)}$, alkoxysulfonyl$_{(C\leq 8)}$, or a substituted version of any of these groups.

In some examples, X_2 is heteroarenediyl$_{(C\leq 12)}$ or substituted heteroarenediyl$_{(C\leq 12)}$. In some examples, X_2 is heteroarenediyl$_{(C\leq 12)}$ such as pyridin-2,4-diyl or pyridine-2,5-diyl. In other examples, X_2 is heterocycloalkanediyl$_{(C\leq 12)}$ or substituted heterocycloalkanediyl$_{(C\leq 12)}$. In some examples, X_2 is heterocycloalkanediyl$_{(C\leq 12)}$ such as piperidin-1,4-diyl, piperazin-1,4-diyl, or 1,2,3,6-tetrahydropiperidin-1,5-diyl. In some examples, p is 0, 1, or 2. In some examples, p is 0. In other examples, p is 1. In other examples, p is 2.

In some examples, R_4''' is acyl$_{(C\leq 8)}$ or substituted acyl$_{(C\leq 8)}$. In some examples, R_4''' is acyl$_{(C\leq 8)}$ such as acetyl. In other examples, R_4''' is amido$_{(C\leq 8)}$ or substituted amido$_{(C\leq 8)}$. In some examples, R_4''' is amido$_{(C\leq 8)}$ such as acetamidyl. In other examples, R_4''' is substituted acyl$_{(C\leq 8)}$ such as carboxy. In other examples, R_4''' is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$. In some examples, R_4''' is cycloalkyl$_{(C\leq 8)}$ such as cyclopropyl. In other examples, R_4''' is alkylsulfonyl$_{(C\leq 8)}$ or substituted alkylsulfonyl$_{(C\leq 8)}$. In some examples, R_4''' is alkylsulfonyl$_{(C\leq 8)}$ such as $-S(O)_2CH_3$ or $-S(O)_2CH_2CH_3$. In other examples, R_4''' is −C(O)−alkoxy$_{(C\leq 8)}$ such as −C(O)OEt. In other examples, R_4''' is −C(O)−dialkylamino$_{(C\leq 8)}$ such as $-C(O)NMe_2$.

In some examples, R_5 is aryl$_{(C\leq 12)}$ or substituted aryl$_{(C\leq 12)}$. In some examples, R_5 is aryl$_{(C\leq 12)}$ such as phenyl, 4-methylphenyl, 3-isopropylphenyl, 4-isopropylphenyl, 1,3-biphenyl, or 1,4-biphenyl. In other examples, R_5 further comprises one or more fluorine atoms. In some examples, R_5 is substituted aryl$_{(C\leq 12)}$ such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 4-hydroxymethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, or 3,4-dichlorophenyl. In other examples, R_5 is cycloalkyl$_{(C\leq 12)}$ or substituted cycloalkyl$_{(C\leq 12)}$ such as cyclopropyl. In other examples, R_5 is cycloalkoxy$_{(C\leq 12)}$ or substituted cycloalkoxy$_{(C\leq 12)}$ such as cyclobutyloxy, cyclopentyloxy, or cyclohexyloxy. In other examples, R_5 is alkylamino$_{(C\leq 12)}$, dialkylamino$_{(C\leq 12)}$, or a substituted version of either of these groups. In some examples, R_5 is dialkylamino$_{(C\leq 12)}$ or substituted dialkylamino$_{(C\leq 12)}$. In some examples, R_5 is dialkylamino$_{(C\leq 8)}$ or substituted dialkylamino$_{(C\leq 8)}$ such as dimethylamino. In other examples, R_5 is alkylsulfonylamino$_{(C\leq 12)}$ or substituted alkylsulfonylamino$_{(C\leq 12)}$ such as methylsulfonylamino. In other examples, R_5 is $-OY_1-A_1$; wherein:

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$.

In some examples, Y_1 is methylene. In some examples, A_1 is cyclobutyl. In some examples, R_5 is:

In other examples, R_5 is $-Y_2-C(O)NR_c-A_2$; wherein:

Y_2 is arenediyl$_{(C\leq 8)}$ or substituted arenediyl$_{(C\leq 8)}$;

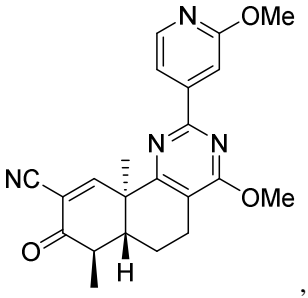
R_c is hydrogen, alkyl$_{(C\leq 6)}$, or substituted alkyl$_{(C\leq 6)}$; and

A_2 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$.

In some examples, Y_2 is arenediyl$_{(C\leq 8)}$ such as benzenediyl. In some examples, R_c is alkyl$_{(C\leq 6)}$ such as methyl. In some examples, A_2 is aralkyl$_{(C\leq 12)}$ such as benzyl.

In other examples, R_5 is heteroaryl$_{(C\leq 12)}$ or substituted heteroaryl$_{(C\leq 12)}$. In some examples, R_5 is heteroaryl$_{(C\leq 12)}$ such as 5-(3-methyl)-oxadiazolyl, 4-(3,5-dimethyl)-isoxazolyl, furanyl, benzofuranyl, 2-thiazolyl, 5-(2-methyl)-furanyl, 3-pyridinyl, or 4-pyridinyl. In other examples, R_5 is hydroxy. In other examples, R_5 is $-OS(O)_2C_6H_4CH_3$. In other examples, R_5 is heterocycloalkyl$_{(C\leq 12)}$ or substituted heterocycloalkyl$_{(C\leq 12)}$. In some examples, R_5 is heterocycloalkyl$_{(C\leq 12)}$ such as pyrrolidinyl. In other examples, R_5 is alkoxy$_{(C\leq 12)}$ or substituted alkoxy$_{(C\leq 12)}$. In some examples, R_5 is alkoxy$_{(C\leq 12)}$ such as methoxy or isopropoxy. In other examples, R_5 is aralkyl$_{(C\leq 12)}$ or substituted aralkyl$_{(C\leq 12)}$. In some examples, R_5 is aralkyl$_{(C\leq 12)}$ such as benzyl.

In some examples, the compounds are further defined as:



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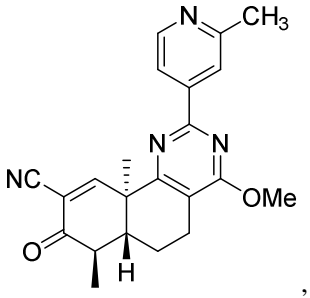

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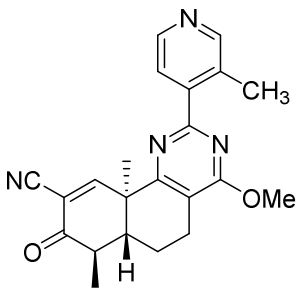

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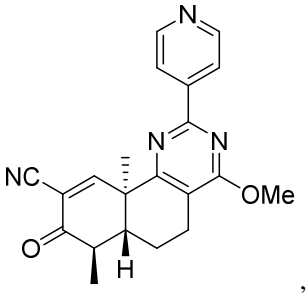

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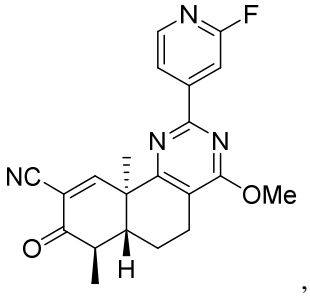

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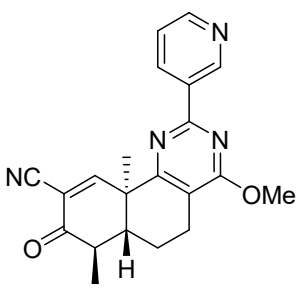

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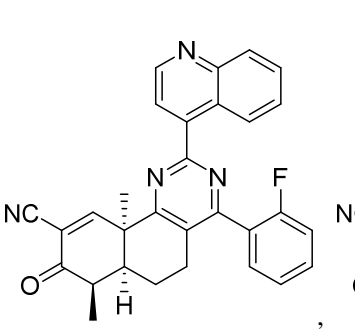
In still another example, the present disclosure provides compounds of the formula: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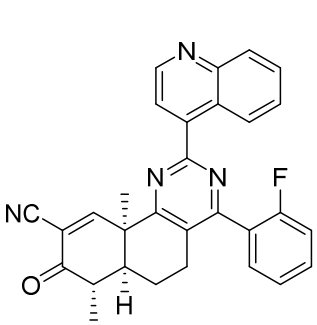
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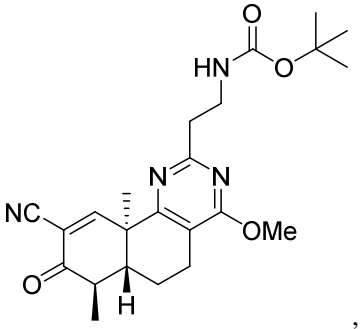
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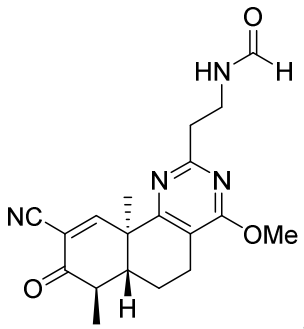
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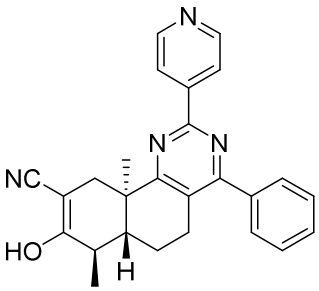
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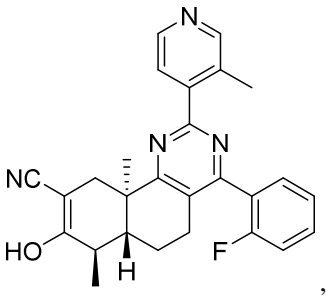
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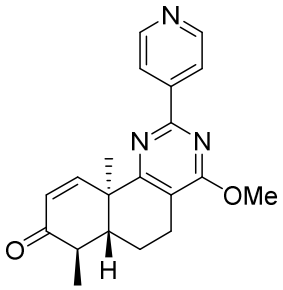
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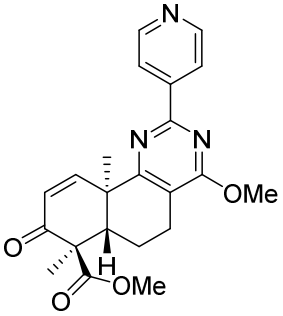
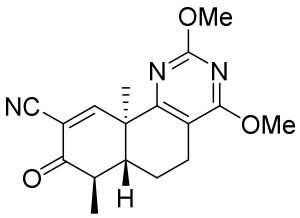

;

or a pharmaceutically acceptable salt thereof.

In yet another example, the present disclosure provides compounds of the formula:



or a pharmaceutically acceptable salt thereof.

In still yet another example, the present disclosure provides compounds further defined as:

(6a*R*,7*R*,10a*S*)-9-cyano-2,4-dimethoxy-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(6a*R*,7*R*,10a*S*)-9-cyano-4-methoxy-2-(2-methoxypyridin-4-yl)-7,10a-dimethyl-5,6a,7,10a-tetrahydrobenzo[*h*]quinazolin-8(*6H*)-one;

(5a*R*,6*R*,9a*S*)-2-(2-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-6,9a-dimethyl-7-oxo-5a,6,7,9a-tetrahydro-5*H*-indeno[1,2-*d*]pyrimidine-8-carbonitrile;

(6a*S*,7*S*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(quinolin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

3-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)propanamide;

N-(2-(4-((6a*R*,7*R*,10a*S*)-9-cyano-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazolin-2-yl)pyridin-2-yl)ethyl)acetamide;

(6a*R*,7*R*,10a*S*)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-2-(3-phenylpyridin-4-yl)-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*R*,7*R*,10a*S*)-2-(3-cyclopropylpyridin-4-yl)-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(6a*S*,7*R*,10a*R*)-2-(2-cyclopropylpyridin-4-yl)-7-ethyl-4-(2-fluorophenyl)-7,10a-dimethyl-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carbonitrile;

(7a*R*,8*R*,11a*S*)-8,11a-dimethyl-2-(2-methylpyridin-4-yl)-9-oxo-4-phenyl-6,7,7a,8,9,11a-hexahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-10-carbonitrile;

(7a*R*,8*R*,11a*S*)-8,11a-dimethyl-9-oxo-4-phenyl-2-(quinolin-5-yl)-6,7,7a,8,9,11a-hexahydro-5*H*-benzo[6,7]cyclohepta[1,2-*d*]pyrimidine-10-carbonitrile;

(6a*R*,7*R*,10a*S*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,10a-hexahydrobenzo[*h*]quinazoline-9-carboxamide;

(6a*R*,7*R*,10a*R*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline-9-carboxamide; and

(6a*R*,7*R*,10a*R*)-4-(4-fluorophenyl)-7,10a-dimethyl-2-(2-methylpyridin-4-yl)-8-oxo-5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazoline-9-carbonitrile;

or a pharmaceutically acceptable salt thereof.

In still another example, the present disclosure provides pharmaceutical compositions comprising:

(A) a compound described herein; and

(B) an excipient.

In some examples, the pharmaceutical compositions are formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularlly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous

infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion. In some examples, the pharmaceutical compositions are formulated for oral administration. In other examples, the pharmaceutical compositions are formulated for administration via injection. In other examples, the pharmaceutical compositions are formulated for intraarterial administration, intramuscular administration, intraperitoneal administration, or intravenous administration. In other examples, the pharmaceutical compositions are formulated for administration topically such as for topical administration to the skin or to the eye. In other examples, the pharmaceutical compositions are formulated as a unit dose.

In yet another example, the present disclosure provides methods of treating or preventing a disease or disorder in a patient in need thereof comprising administering to the patient a pharmaceutically effective amount of a compound or composition described herein. In some examples, the patient is a mammal such as a human. In some examples, the disease or disorder is associated with increased production of cytokine IL-17. In some examples, the disease or disorder is associated with dysregulated angiogenesis.

In some examples, the disease or disorder is an autoimmune disease, organ rejection, asthma, cancer, a neurological disorder, a psychiatric disorder, a neuropsychiatric disorder, chronic pain syndrome, an inflammatory condition, a retinal disorder, or a cardiovascular disease. In some examples, the disease or disorder is cancer In some examples, the disease or disorder is an autoimmune disease such as psoriasis, multiple sclerosis, scleroderma, rheumatoid arthritis, lupus, psoriatic arthritis, ankylosing spondylitis, Sjögren syndrome, vitiligo, uveitis, dry eye syndrome, systemic sclerosis, type 1 diabetes, myasthenia gravis, and inflammatory bowel disease. In other examples, the disease or disorder is a cardiovascular disease such as vasculitis, atherosclerosis, myocardial infarction, myocarditis, heart failure, pulmonary hypertension, or stroke. In other examples, the disease or disorder is a neurological disorder such as epilepsy, multiple sclerosis, spinal cord injury, Guillain-Barre syndrome, or another neurological disorder involving dysregulated inflammatory signaling. In other examples, the disease or disorder is a neurodegenerative disorder such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease. In other examples, the disease or disorder is an inflammatory condition such as pancreatitis, hepatitis, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, dermatitis, gastritis, esophagitis, irritable bowel syndrome, inflammatory bowel disease, nephritis, muscle wasting, or osteoarthritis. In other examples, the disease or disorder is a chronic pain syndrome such as fibromyalgia or neuropathic pain. In other examples, the disease or disorder is a severe inflammatory response to a pathogen such as from encephalitis, meningitis, *H. pylori*, *Toxoplasma gondii*, or *Leishmania spp.* In other examples, the disease or disorder is obesity or a condition associated with obesity. In some examples, the condition associated with obesity is insulin resistance or fatty liver disease. In some examples, the retinal disorder is macular degeneration or another disorder of the retina.

In some examples, the disease or disorder is associated with inflammation. In some examples, the disease or disorder associated with inflammation is obesity, Type 2 diabetes, or a

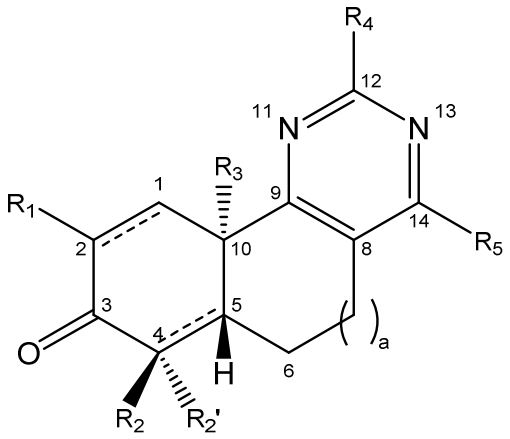
complication of Type 1 or Type 2 diabetes. In some examples, the complication of Type 1 or Type 2 diabetes is neuropathy, reduced kidney function or chronic kidney disease, retinopathy, diabetic ulcers, or cardiovascular disease. In other examples, the disease or disorder associated with inflammation is chronic kidney disease. In some examples, the chronic kidney disease is hereditary. In other examples, the chronic kidney disease is due to a non-hereditary cause.

In some examples, the methods comprise administering the compound once. In other examples, the methods comprise administering the compound two or more times.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples of the 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.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(I)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

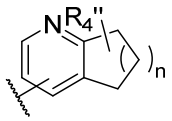
R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of any of these groups, or −alkanediyl$_{(C\leq 8)}$−cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, or alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, 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$_{(C\leq 12)}$, or a substituted version of these groups; provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, aryl$_{(C\leq 18)}$, substituted aryl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, or


;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $alkylamino_{(C\leq 8)}$, $dialkylamino_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; or

$$-X_2-(CH_2)_p-R_4'''$$;

wherein:

X_2 is $arenediyl_{(C\leq 12)}$, substituted $arenediyl_{(C\leq 12)}$, $heterocycloalkanediyl_{(C\leq 12)}$, substituted $heterocycloalkanediyl_{(C\leq 12)}$, $heteroarenediyl_{(C\leq 12)}$, or substituted $heteroarenediyl_{(C\leq 12)}$;

p is 0, 1, 2, 3, or 4; and

R_4''' is $alkyl_{(C\leq 8)}$, $cycloalkyl_{(C\leq 8)}$, $aryl_{(C\leq 8)}$, $heteroaryl_{(C\leq 8)}$, $heterocycloalkyl_{(C\leq 8)}$, $acyl_{(C\leq 8)}$, $amido_{(C\leq 8)}$, $alkoxy_{(C\leq 8)}$, $acyloxy_{(C\leq 8)}$, $-C(O)-alkoxy_{(C\leq 8)}$, $-C(O)-alkylamino_{(C\leq 8)}$, $-C(O)-dialkyl\text{-}amino_{(C\leq 8)}$, $alkylsulfonyl_{(C\leq 8)}$, $arylsulfonyl_{(C\leq 8)}$, $alkoxysulfonyl_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is amino, hydroxy, isopropoxy, $-OS(O)_2C_6H_4CH_3$, $alkyl_{(C\leq 12)}$, $cycloalkyl_{(C\leq 12)}$, $cycloalkoxy_{(C\leq 12)}$, $aryl_{(C\leq 12)}$, $aralkyl_{(C\leq 12)}$, $heteroaryl_{(C\leq 12)}$, $heteroaralkyl_{(C\leq 12)}$, $heterocycloalkyl_{(C\leq 12)}$, $acyl_{(C\leq 12)}$, $acyloxy_{(C\leq 12)}$, $alkylamino_{(C\leq 12)}$, $dialkylamino_{(C\leq 12)}$, $alkylsulfonylamino_{(C\leq 12)}$, or a substituted version of any of the last thirteen groups, or

$$-OY_1-A_1$$;

wherein:

Y_1 is $alkanediyl_{(C\leq 8)}$ or substituted $alkanediyl_{(C\leq 8)}$; and

A_1 is $cycloalkyl_{(C\leq 8)}$ or substituted $cycloalkyl_{(C\leq 8)}$; or

$$-Y_2-C(O)NR_c-A_2$$;

wherein:

Y_2 is $arenediyl_{(C\leq 8)}$ or substituted $arenediyl_{(C\leq 8)}$;

R_c is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

A_2 is $aralkyl_{(C\leq 12)}$ or substituted $aralkyl_{(C\leq 12)}$; or

$-A_3R_d$;

wherein:

A_3 is $-O-$ or $-NR_e-$, wherein

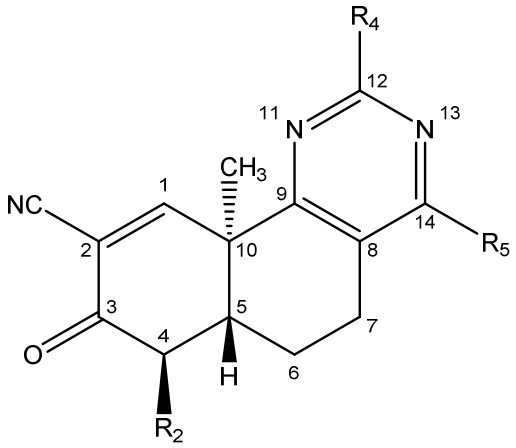
R_e is hydrogen, $alkyl_{(C\leq 6)}$, or substituted $alkyl_{(C\leq 6)}$; and

R_d is $acyl_{(C\leq 12)}$, or substituted $acyl_{(C\leq 12)}$;

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 further defined as:



(VII)

wherein:

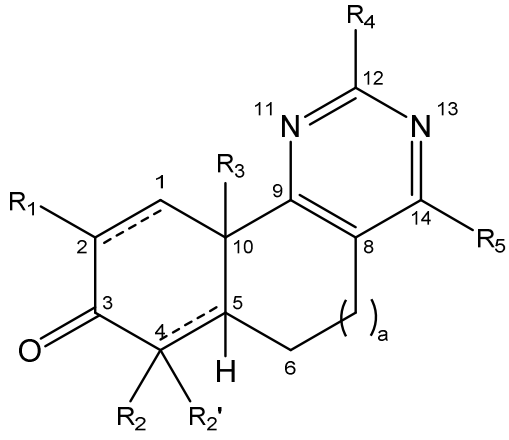
R_2 is hydrogen, $alkyl_{(C\leq 12)}$, or substituted $alkyl_{(C\leq 12)}$;

R_4 is $heteroaryl_{(C\leq 18)}$ or substituted $heteroaryl_{(C\leq 18)}$; and

R_5 is $aryl_{(C\leq 12)}$ or substituted $aryl_{(C\leq 12)}$;

or a pharmaceutically acceptable salt thereof.

3. A compound of the formula:



(X)

wherein:

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

the bond between carbon atoms 4 and 5 is a single bond or a double bond;

a is 0, 1, or 2;

R_1 is cyano, heteroaryl$_{(C\leq 8)}$, substituted heteroaryl$_{(C\leq 8)}$, $-CF_3$, or $-C(O)R_a$; wherein:

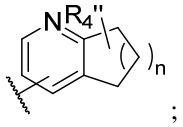
R_a is hydroxy, amino, or alkoxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, alkylsulfonylamino$_{(C\leq 8)}$, or a substituted version of any of these groups;

R_2 is hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, or −alkanediyl$_{(C\leq 8)}$−cycloalkyl$_{(C\leq 12)}$ or a substituted version of this group;

R_2' is absent, hydrogen, alkyl$_{(C\leq 12)}$, cycloalkyl$_{(C\leq 12)}$, alkenyl$_{(C\leq 12)}$, alkynyl$_{(C\leq 12)}$, or a substituted version of the last four groups, provided that when the bond between carbon atoms 4 and 5 is a double bond then R_2' is absent;

R_3 is alkyl$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, aralkyl$_{(C\leq 12)}$, or a substituted version of any of these groups;

R_4 is cycloalkyl$_{(C\leq 18)}$, substituted cycloalkyl$_{(C\leq 18)}$, heteroaryl$_{(C\leq 18)}$, substituted heteroaryl$_{(C\leq 18)}$, heterocycloalkyl$_{(C\leq 18)}$, substituted heterocycloalkyl$_{(C\leq 18)}$, or



;

wherein:

n is 0, 1, 2, 3, or 4; and

R_4'' is −H, −OH, −F, −Cl, −Br, −I, $-NH_2$, $-NO_2$, −CN, −SH, $-S(O)_2OH$, or $-S(O)_2NH_2$, or alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, amido$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, alkylamino$_{(C\leq 8)}$, dialkylamino$_{(C\leq 8)}$, −C(O)−alkoxy$_{(C\leq 8)}$, −C(O)−alkylamino$_{(C\leq 8)}$, −C(O)−dialkyl-amino$_{(C\leq 8)}$, alkylsulfonyl$_{(C\leq 8)}$, arylsulfonyl$_{(C\leq 8)}$, alkoxysulfonyl$_{(C\leq 8)}$, or a substituted version of any of these groups; or

$-X_2-(CH_2)_p-R_4'''$;

wherein:

X_2 is arenediyl$_{(C\leq 12)}$, substituted arenediyl$_{(C\leq 12)}$, heterocycloalkyldiyl$_{(C\leq 12)}$, substituted heterocycloalkyldiyl$_{(C\leq 12)}$, heteroarenediyl$_{(C\leq 12)}$, or substituted heteroarenediyl$_{(C\leq 12)}$;

p is 0, 1, 2, 3, or 4; and

R_4''' is alkyl$_{(C\leq 8)}$, cycloalkyl$_{(C\leq 8)}$, aryl$_{(C\leq 8)}$, heteroaryl$_{(C\leq 8)}$, heterocycloalkyl$_{(C\leq 8)}$, acyl$_{(C\leq 8)}$, alkoxy$_{(C\leq 8)}$, acyloxy$_{(C\leq 8)}$, −C(O)−alkoxy$_{(C\leq 8)}$,

−C(O)−alkylamino$_{(C\leq 8)}$, −C(O)−dialkyl-amino$_{(C\leq 8)}$, alkylsulfonyl$_{(C\leq 8)}$, arylsulfonyl$_{(C\leq 8)}$, alkoxysulfonyl$_{(C\leq 8)}$, or a substituted version of any of these groups; and

R_5 is cycloalkoxy$_{(C\leq 12)}$, aryl$_{(C\leq 12)}$, heteroaryl$_{(C\leq 12)}$, or a substituted version of any of the last three groups, or

$$-OY_1-A_1;$$

wherein:

Y_1 is alkanediyl$_{(C\leq 8)}$ or substituted alkanediyl$_{(C\leq 8)}$; and

A_1 is cycloalkyl$_{(C\leq 8)}$ or substituted cycloalkyl$_{(C\leq 8)}$; or

provided that when carbon atoms 4 and 5 are joined by a double bond, then R_2' and the hydrogen atom at carbon atom 5 are absent;

or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1-3, wherein R_1 is cyano.

5. The compound according to any one of claims 1-4, wherein R_2 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$.

6. The compound according to any one of claims 1-5, wherein R_2' is hydrogen, alkyl$_{(C\leq 12)}$, or substituted alkyl$_{(C\leq 12)}$, or R_3 is alkyl$_{(C\leq 12)}$ or substituted alkyl$_{(C\leq 12)}$.

7. The compound according to any one of claims 1-6, wherein R_4 is heteroaryl$_{(C\leq 18)}$ or substituted heteroaryl$_{(C\leq 18)}$.

8. The compound of claim 7, wherein R_4 is a heteroaryl$_{(C\leq 12)}$ or a substituted heteroaryl$_{(C\leq 12)}$ group wherein at least one of the heteroatoms in the aromatic ring is a nitrogen atom.

9. The compound of claim 7, wherein R_4 is heteroaryl$_{(C\leq 18)}$.

10. The compound of claim 7, wherein R_4 is 3-pyridinyl, 4-pyridinyl, 4-(2-cycylopropyl)-pyridinyl, 5-(2-cycylopropyl)-pyridinyl, 4-(2-morpholino)-pyridinyl, 4-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 3-(6-methyl)-pyridinyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-pyrazolo[1,5-*a*]pyridinyl, 3-(*N*-methyl)-pyrrolo[2,3-*b*]pyridinyl, 5-isoquinlinyl, 2-isoquinlinyl, 1-isoquinolinyl, 4-(2-phenyl)-pyridinyl, 5-(2-phenyl)-pyridinyl, 3-(5-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 4-(3,5-dimethyl)-isoxazolyl, 4-(2-methyl)-pyridinyl, 4-(3-methyl)-pyridinyl, 3-(4-methyl)-pyridinyl, 4-(6-methyl)-pyrimidinyl, 6-(4-methyl)-pyrimidinyl, 4-pyridazinyl, 2-quinazolinyl, 4-quinazolinyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 5-quinolinyl, 6-quinolinyl, 8-quinolinyl, 4-isoquinolinyl, 3-(8-methyl)-quinolinyl, 3-(1-methyl)-quinolinyl, 4-(2-methyl)-quinolinyl, 4-(2-isopropyl)-quinolinyl, 4-(6-methyl)-quinolinyl, 4-(7-methyl)-quinolinyl, 4-(8-methyl)-quinolinyl, 2-(*N*-methyl)-indolyl, 5-(2,4-dimethyl)-thiazolyl, or 5-(3-methyl)-oxadizolyl.

11. The compound of claim 7, wherein R_4 is substituted heteroaryl$_{(C\leq18)}$.

12. The compound of claim 11, wherein R_4 is 4-(2-trifluoromethyl)-pyridinyl, 4-(3-fluoro)-pyridinyl, 4-(2-methoxy)-pyridinyl, 4-(2-hydroxymethyl)-pyridinyl, 4-(2-acetylamino)-pyridinyl, 4-(2-fluoromethyl)-pyridinyl, 4-(2-acetamidylethyl)-pyridinyl, 4-(2-fluoromethyl)-quinolinyl, 4-(2-acetoxymethyl)-quinolinyl, 4-(2-formyl)-quinolinyl, 4-(6-fluoro)-quinolinyl, 4-(7-fluoro)-quinolinyl, 4-(8-fluoro)-quinolinyl, 4-(6,8-difluoro)-quinolinyl, 4-(6-fluoro-2-methyl)-quinolinyl, or 4-(8-fluoro-2-methyl)-quinolinyl.

13. The compound according to any one of claims 1-6, wherein R_4 is aryl$_{(C\leq12)}$ or substituted aryl$_{(C\leq12)}$.

14. The compound according to any one of claims 1-13, wherein R_5 is aryl$_{(C\leq12)}$ or substituted aryl$_{(C\leq12)}$.

15. The compound of claim 14, wherein R_5 is aryl$_{(C\leq12)}$.

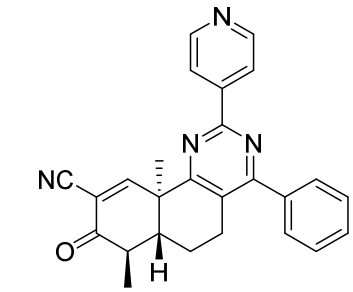
16. The compound of claim 14, wherein R_5 is phenyl, 4-methylphenyl, 3-isopropylphenyl, 4-isopropylphenyl, 1,3-biphenyl, or 1,4-biphenyl.

17. The compound of claim 14, wherein R_5 is a substituted aryl$_{(C\leq12)}$ wherein one or more hydrogen atoms of the aryl$_{(C\leq12)}$ has been independently replaced by –F.

18. The compound of claim 14, wherein R_5 is substituted aryl$_{(C\leq12)}$.

19. The compound of claim 18, wherein R_5 is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 4-hydroxymethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, or 3,4-dichlorophenyl.

20. The compound according to any one of claims 1-3, wherein the compound is further defined as: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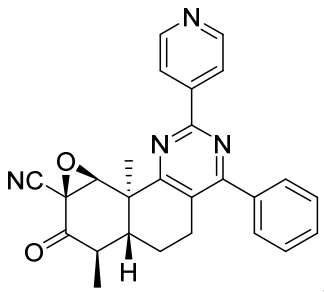
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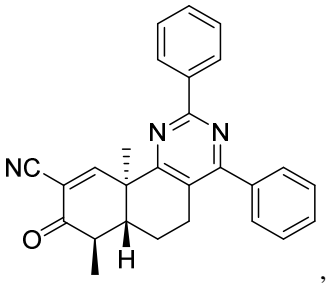
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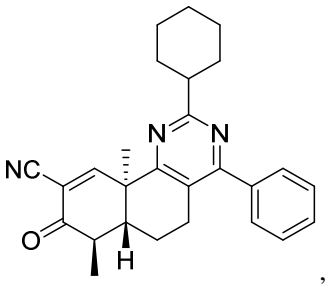
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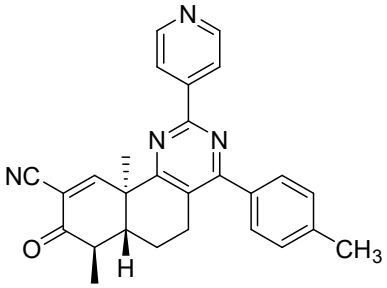
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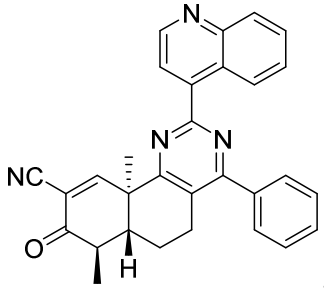
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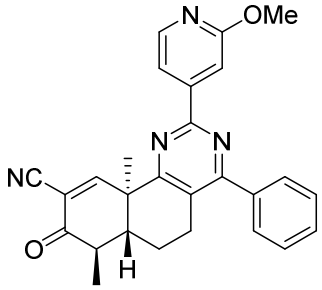
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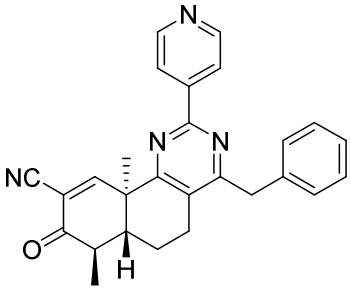
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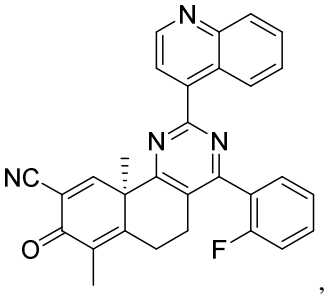
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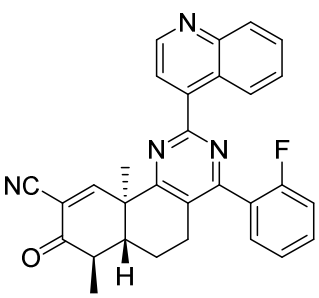
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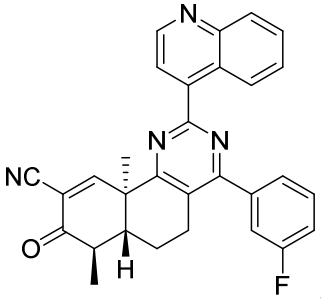
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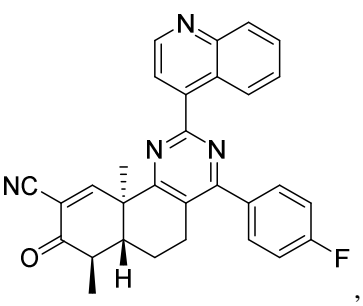
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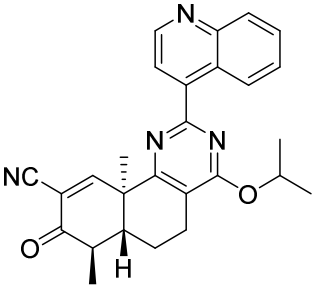
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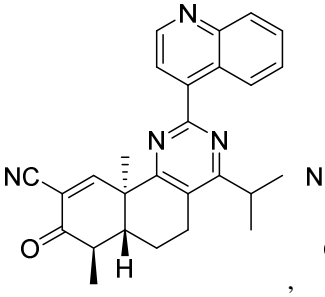
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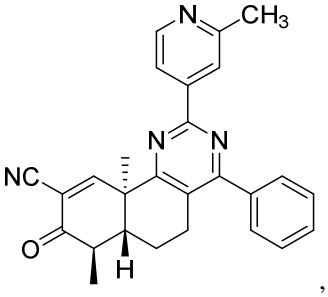
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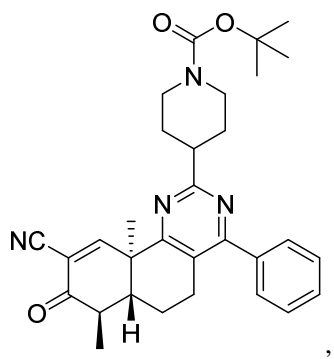
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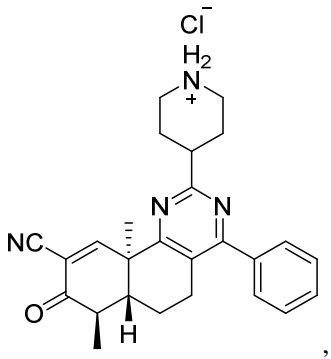
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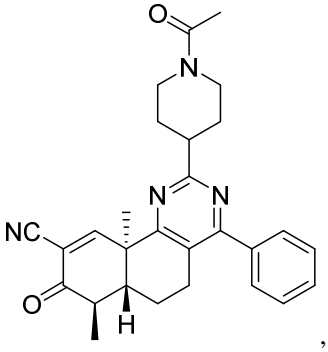
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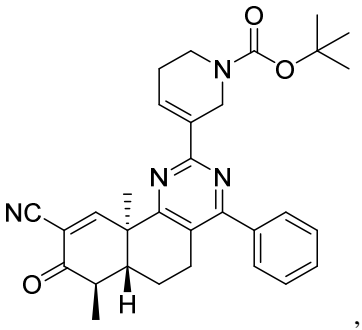
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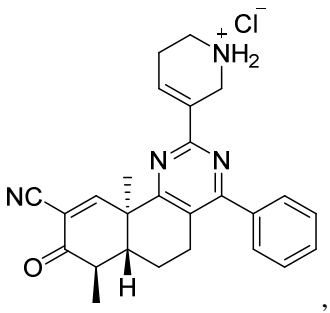
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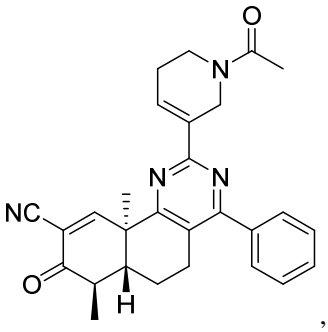
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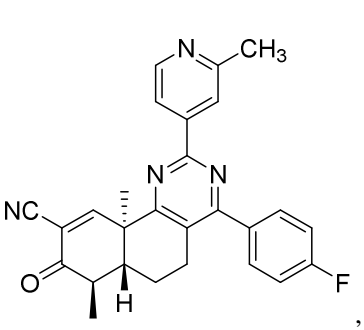
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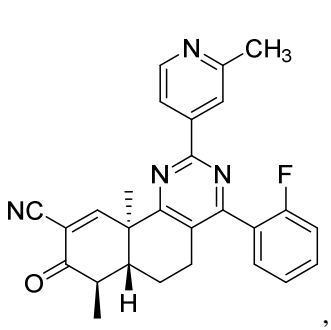
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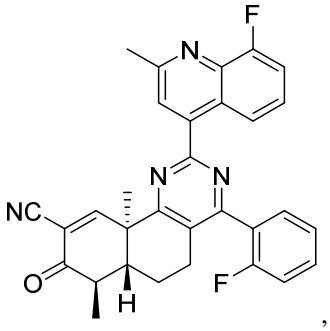
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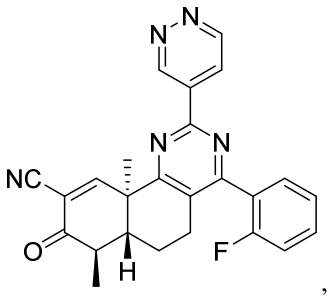
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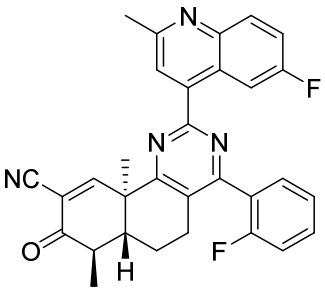
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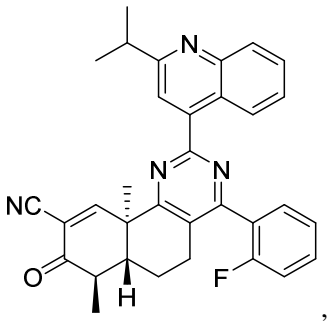
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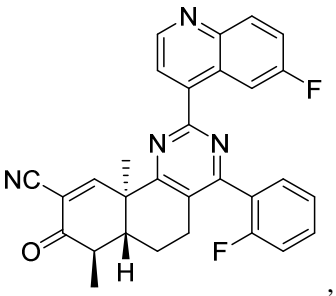
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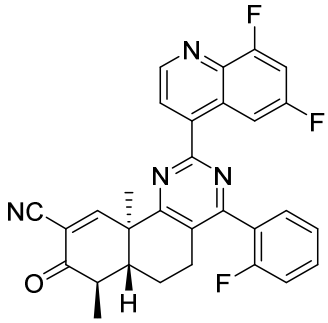
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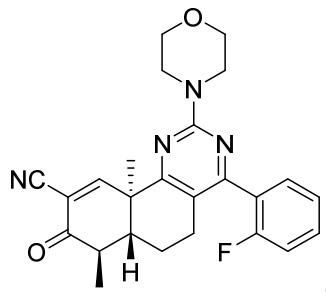
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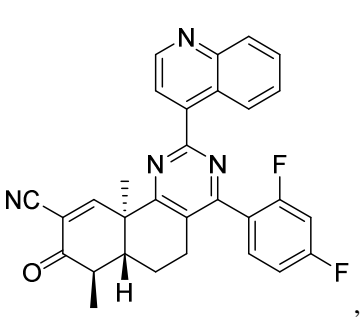
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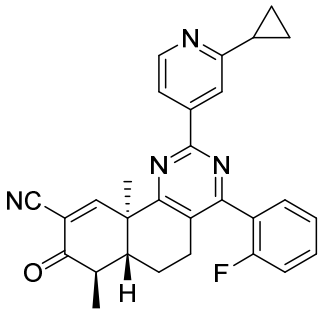
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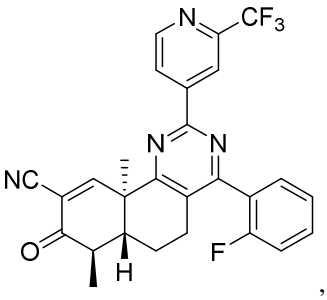
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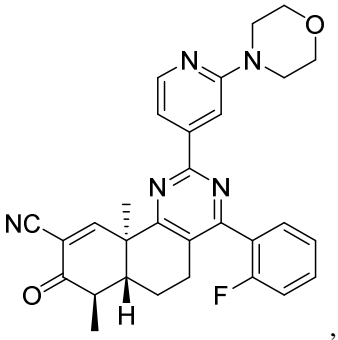
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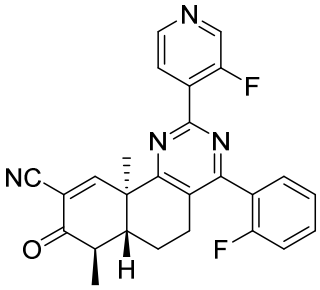
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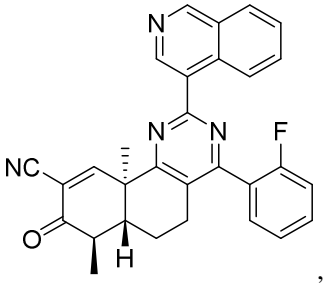
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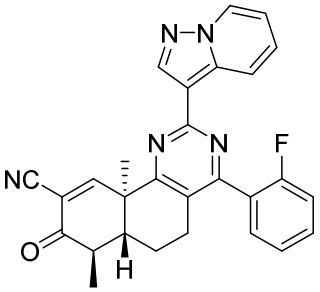
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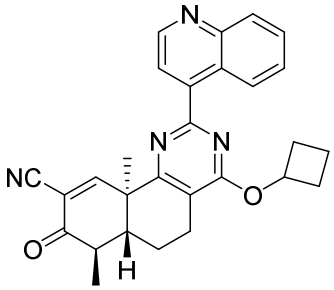
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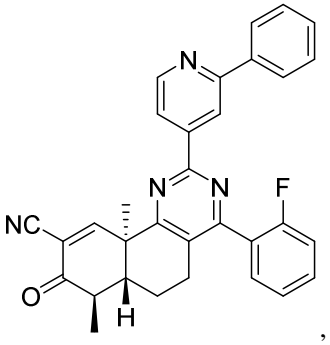
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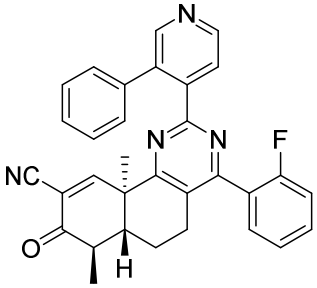
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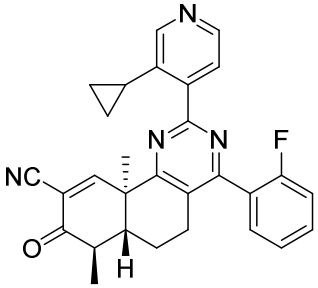
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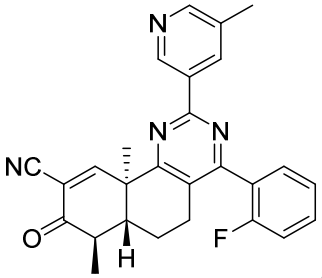
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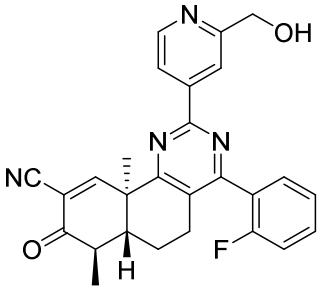
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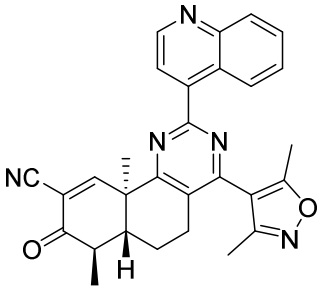
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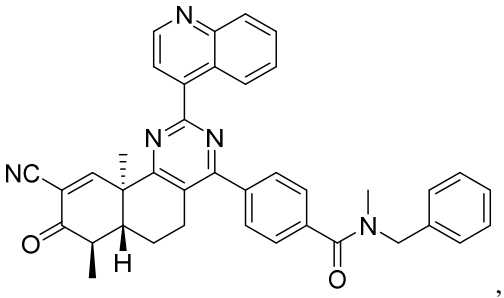
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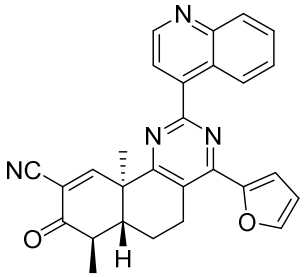
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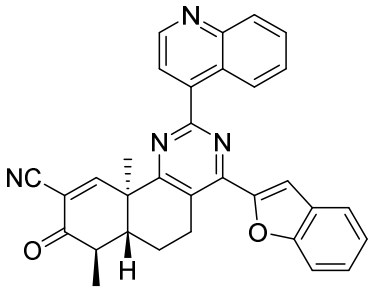
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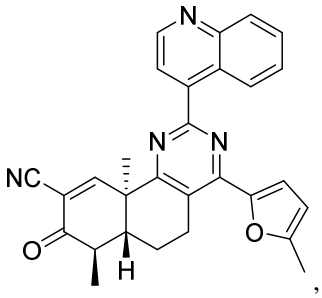
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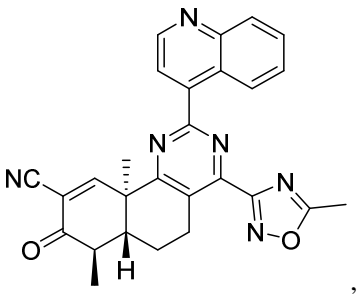
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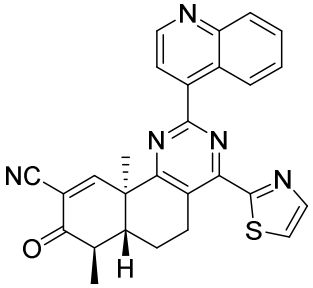
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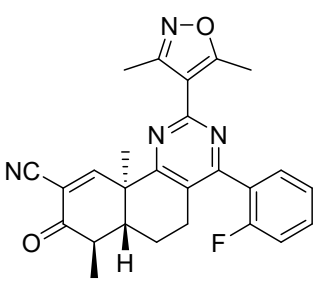
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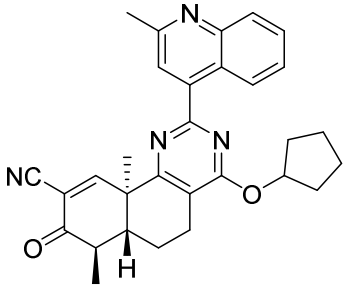
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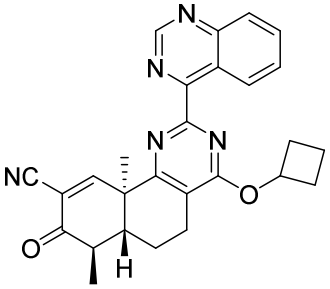
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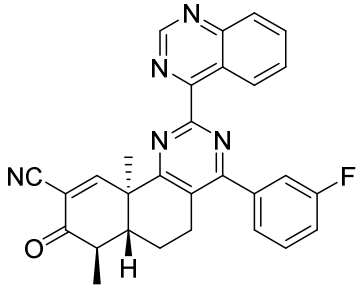
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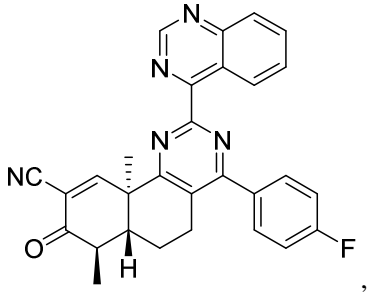
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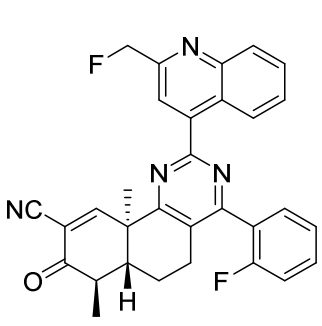
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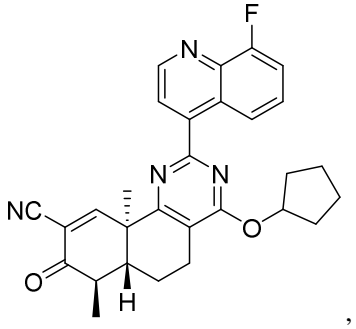
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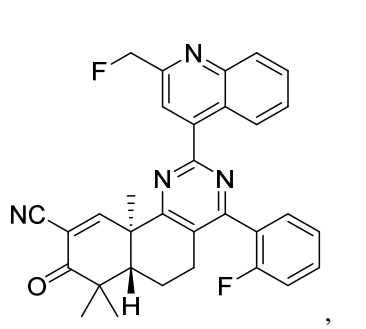
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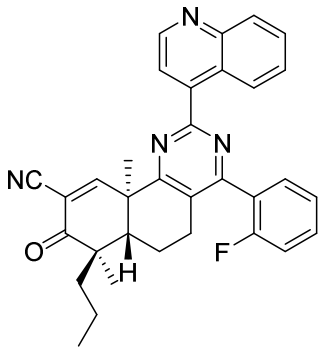
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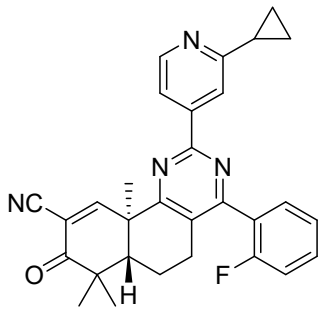
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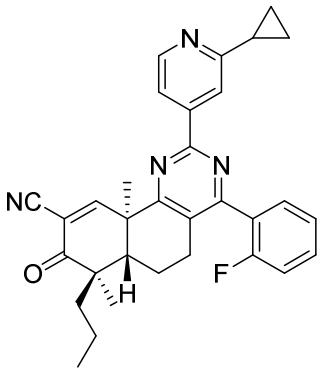
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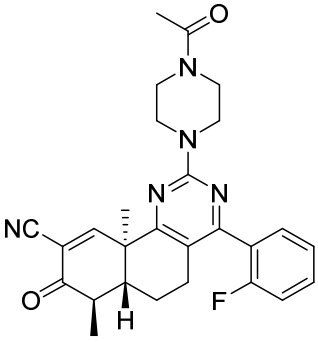
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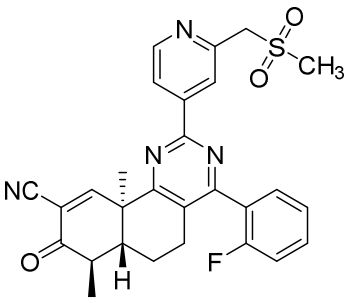
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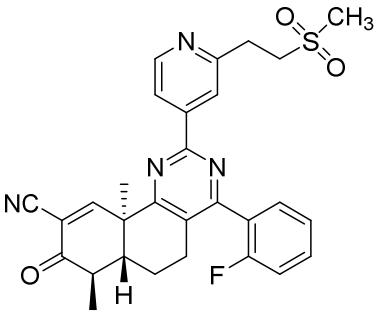
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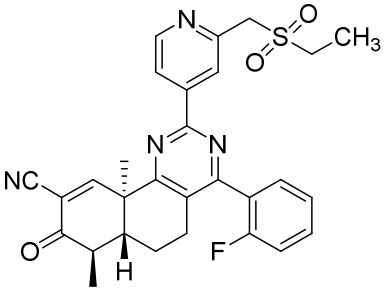
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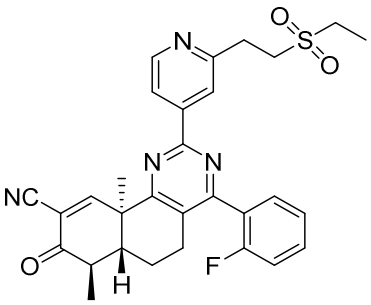
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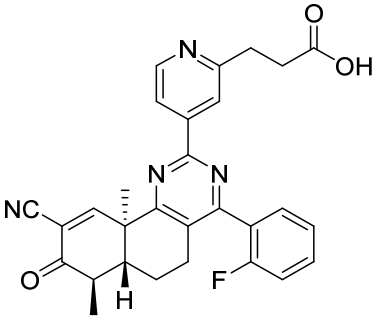
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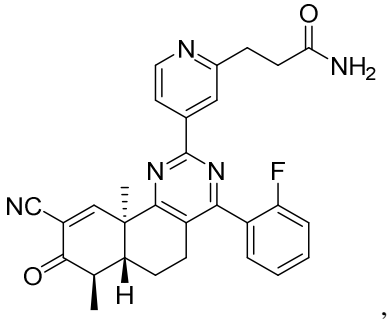
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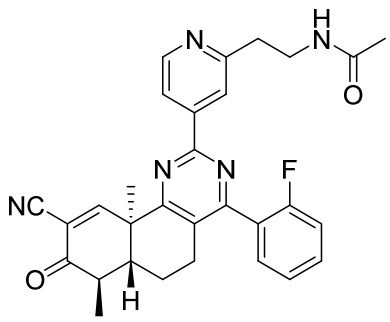
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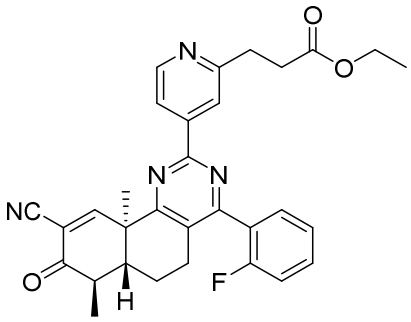
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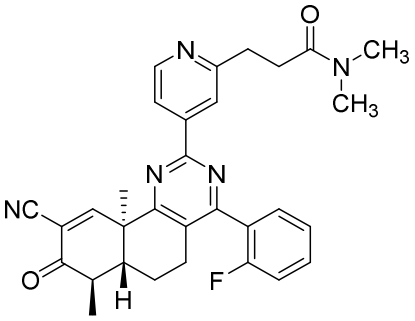
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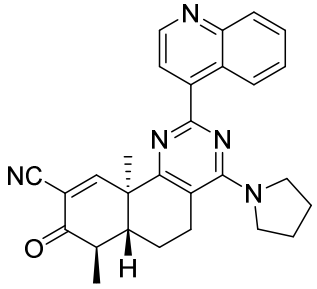
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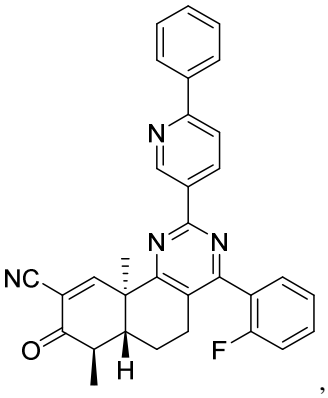
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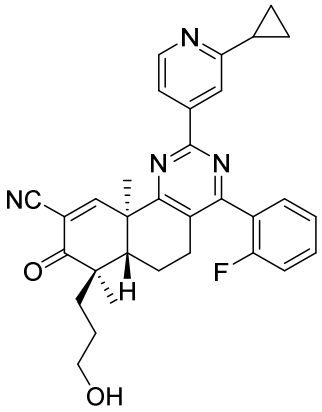
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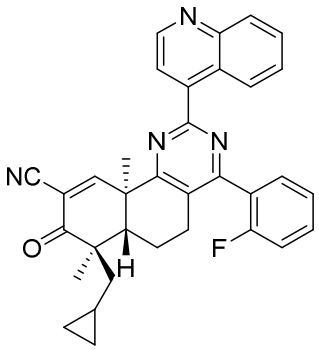
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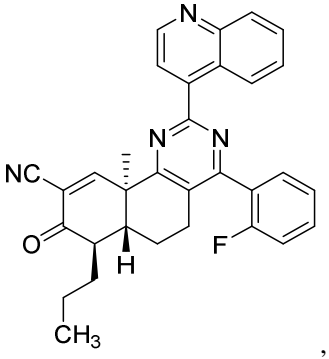
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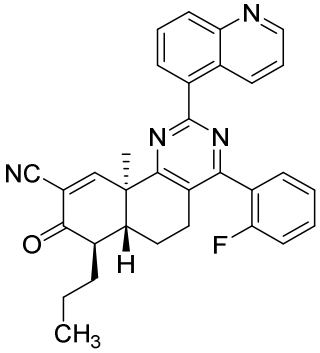
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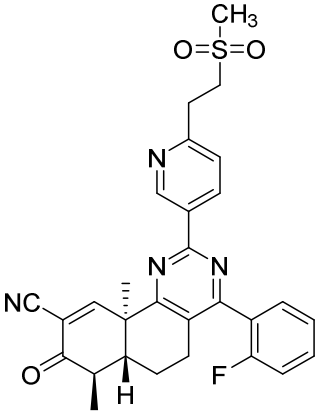
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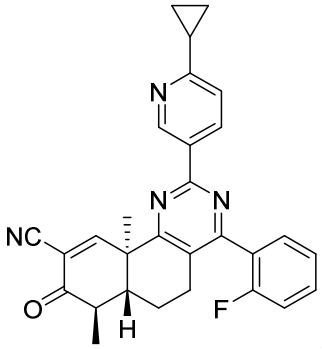
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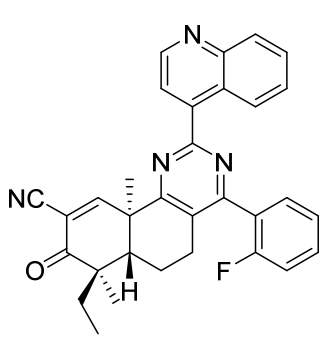
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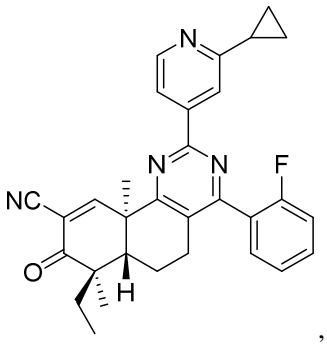
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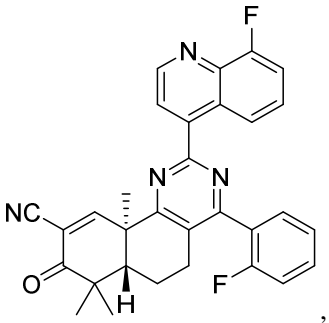
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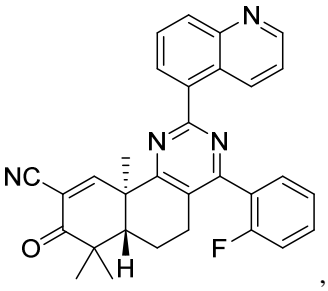
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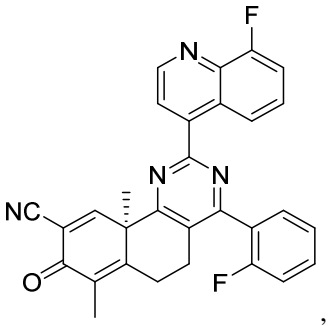
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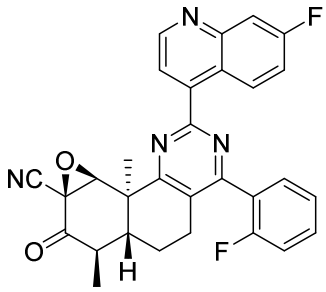
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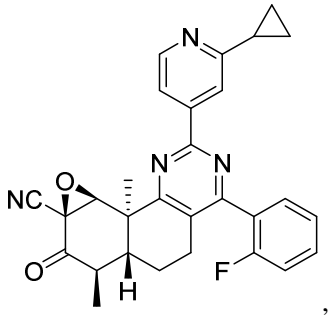
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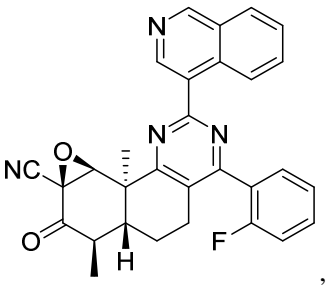
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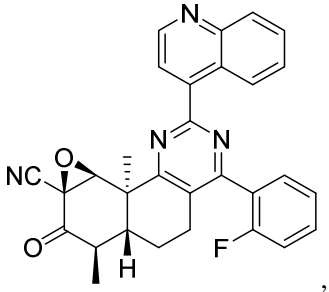
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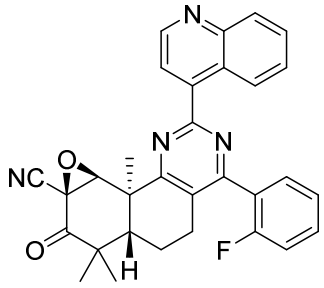
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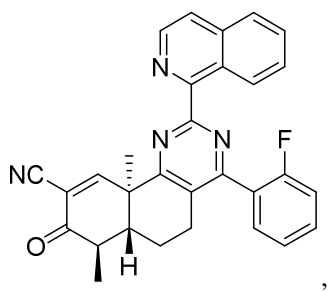
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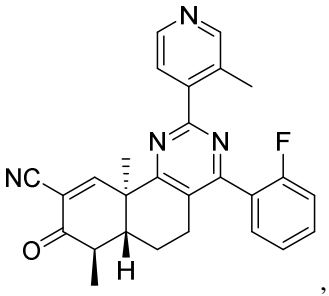
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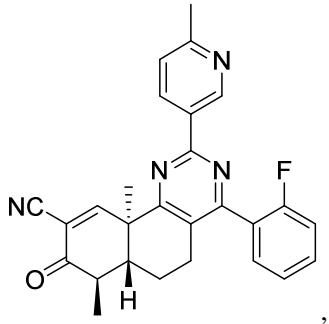
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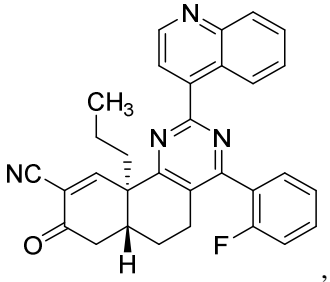
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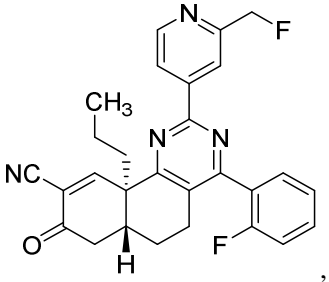
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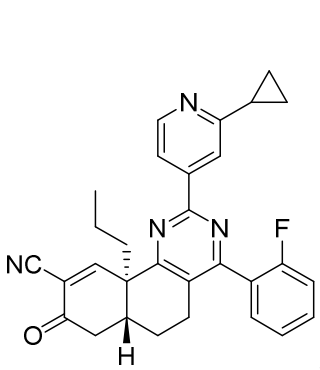
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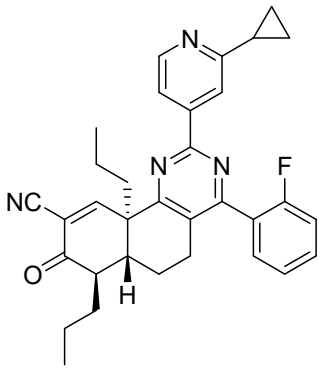
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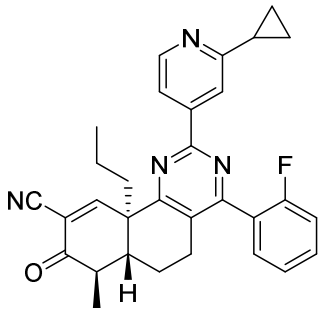
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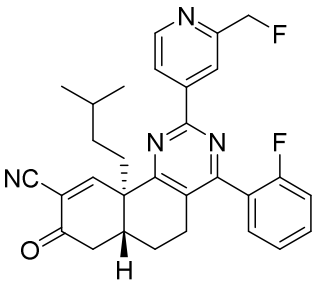
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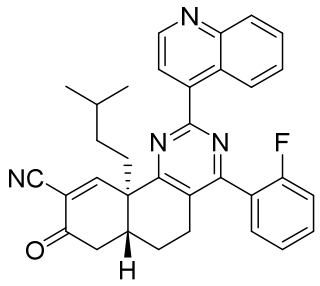
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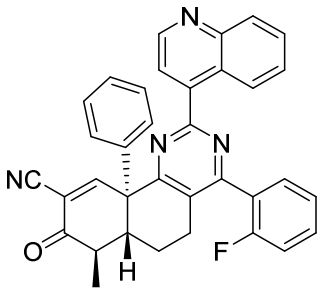
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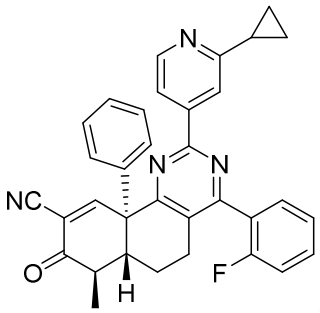
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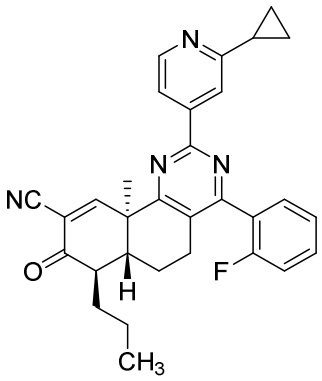
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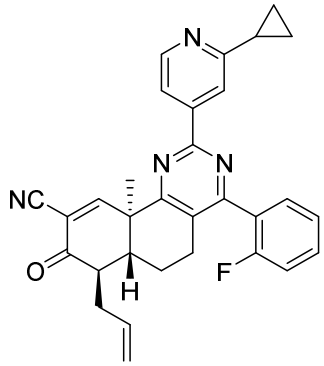
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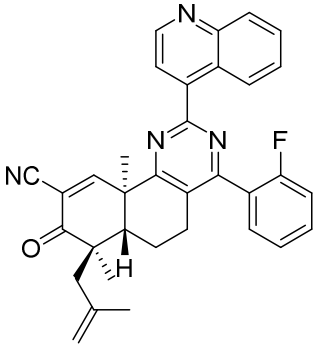
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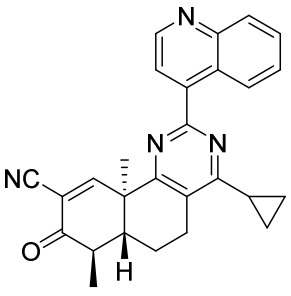
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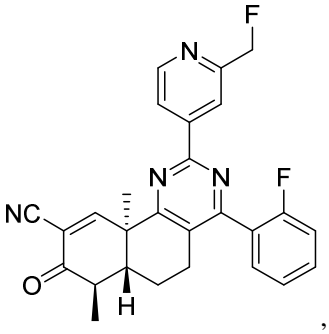
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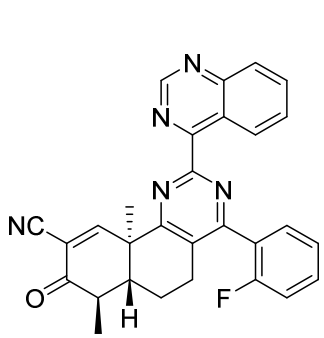
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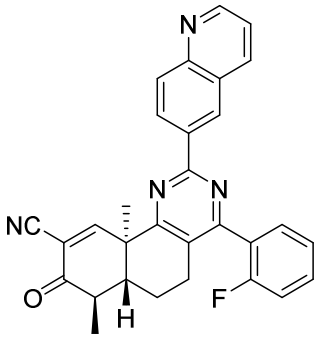
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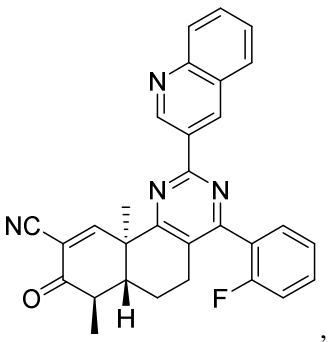
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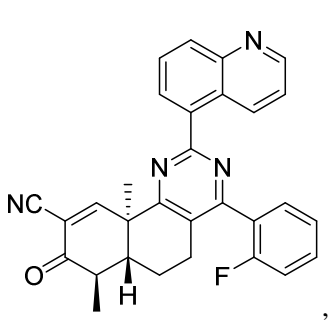
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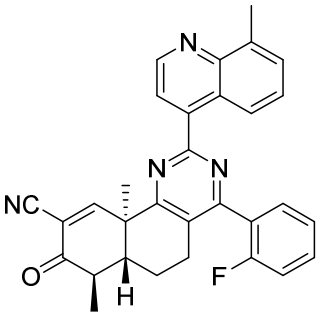
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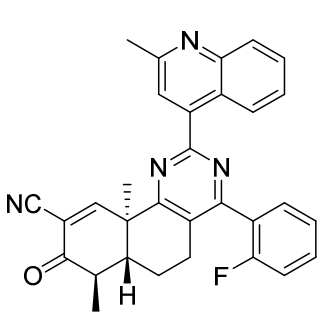
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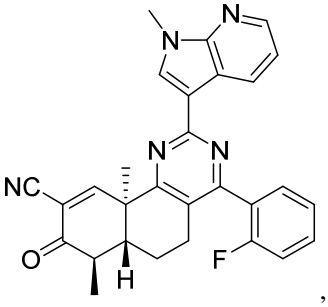
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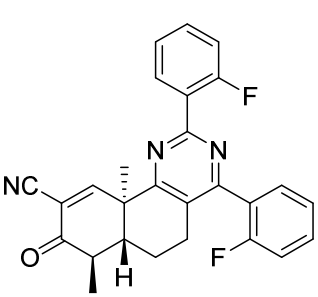
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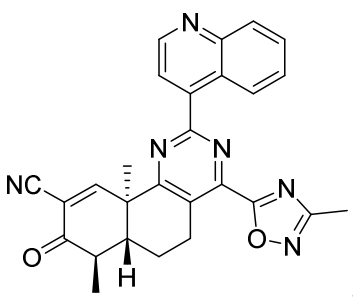
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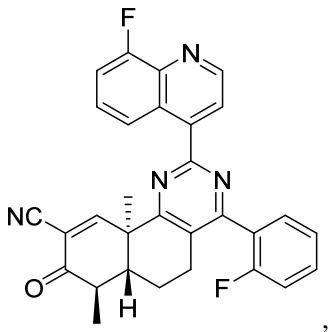
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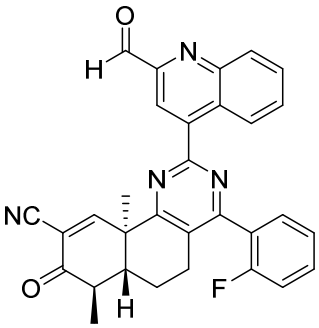
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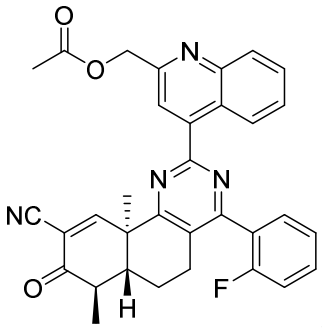
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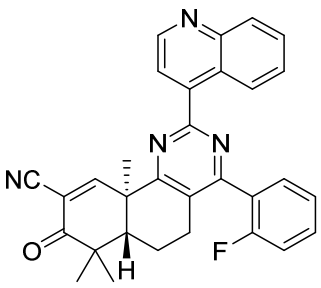
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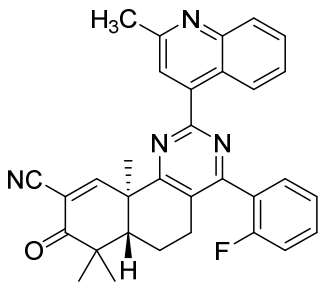
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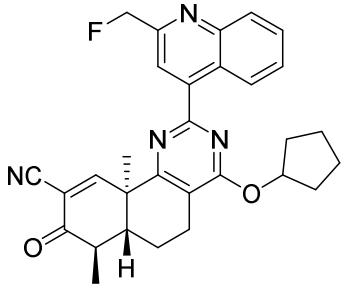
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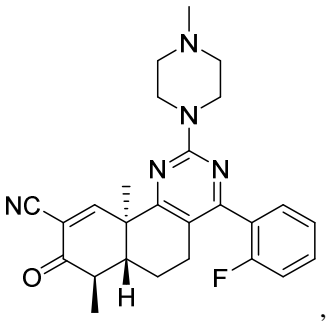
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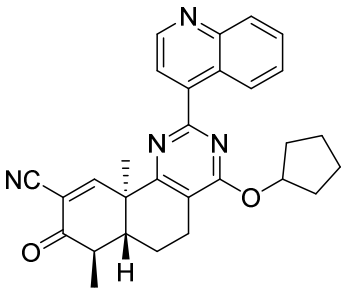
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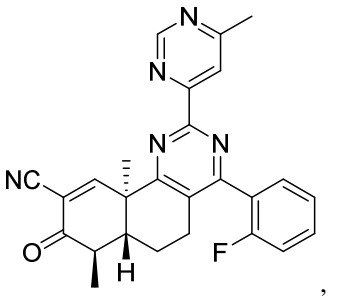
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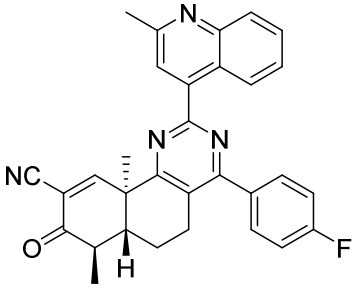
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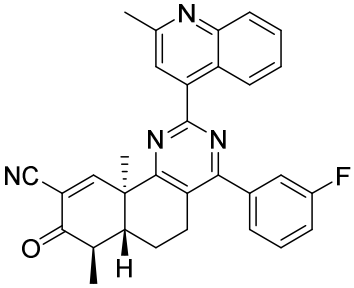
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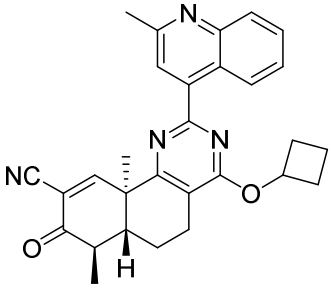
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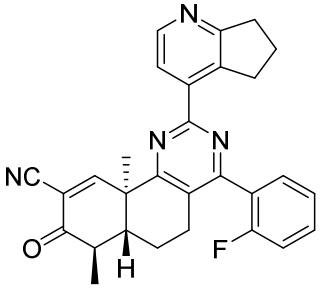
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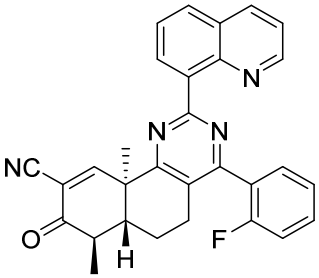
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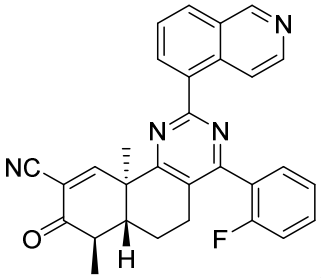
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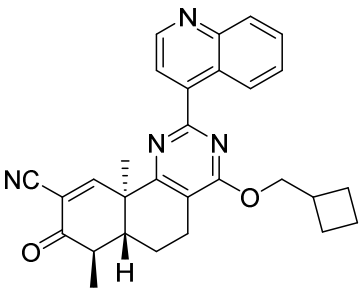
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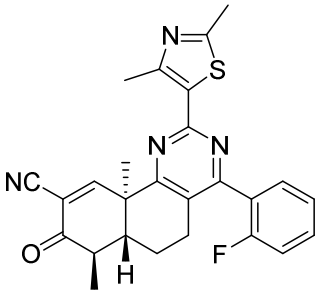
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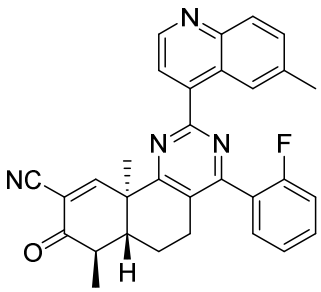
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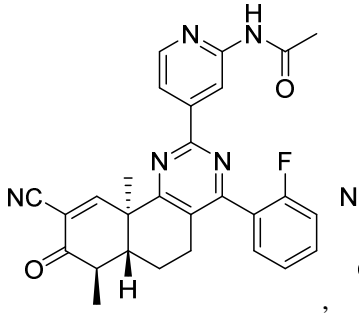
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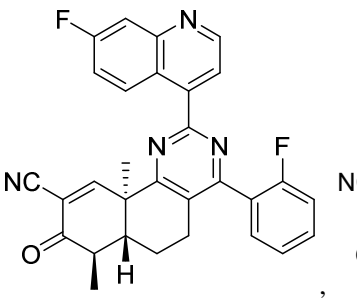
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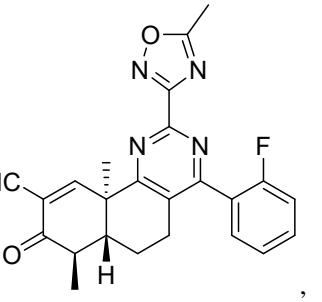
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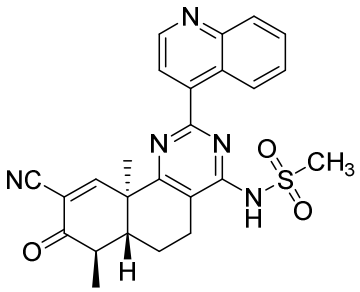
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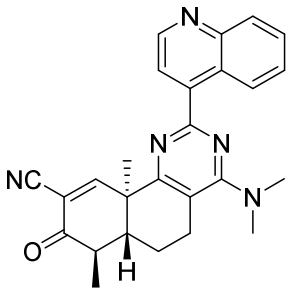
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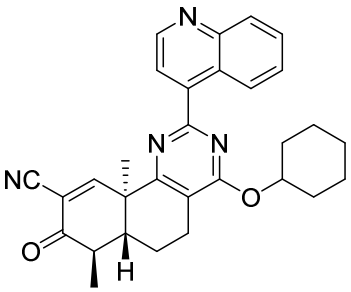
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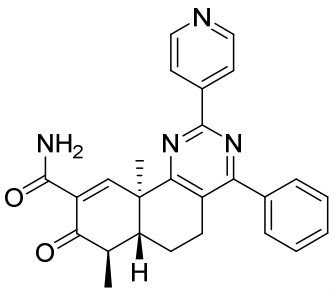
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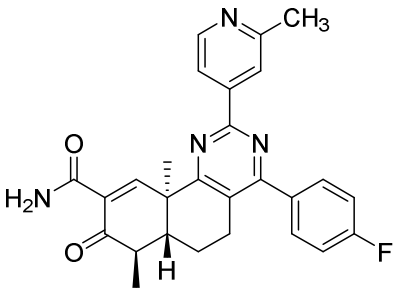
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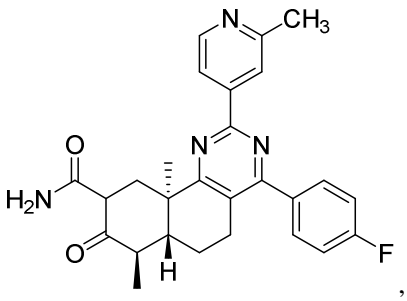
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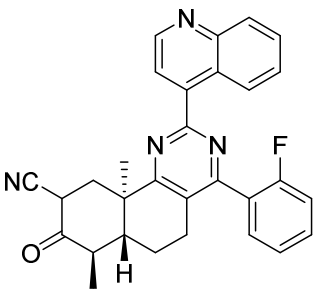
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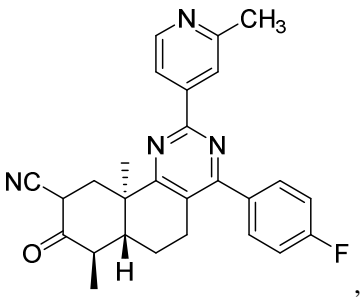
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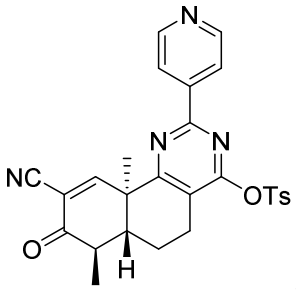
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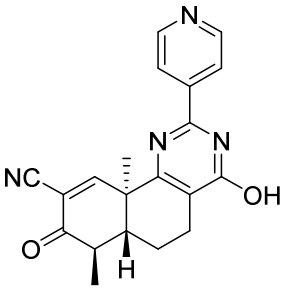
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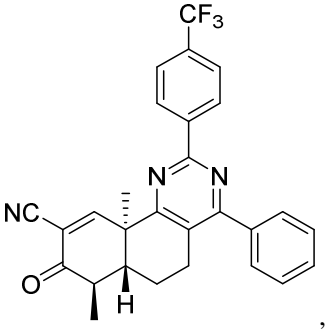
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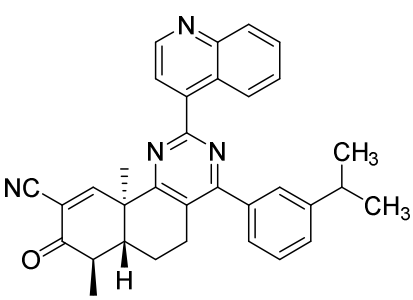
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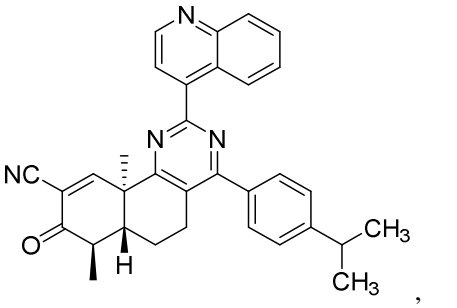
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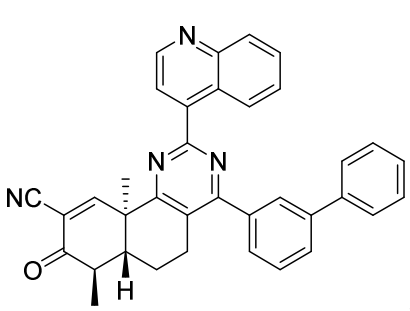
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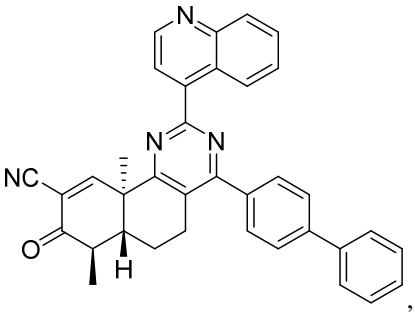
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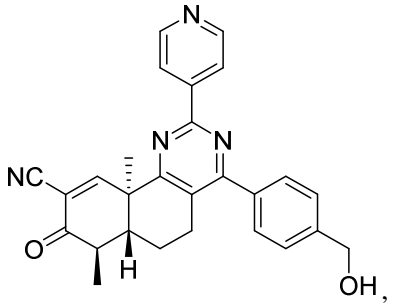
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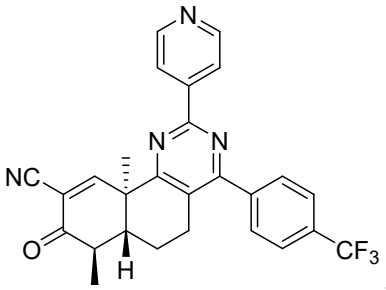
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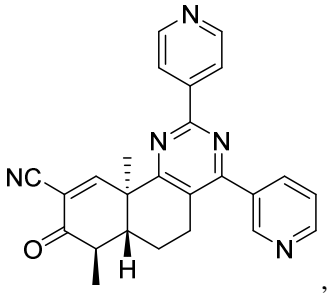
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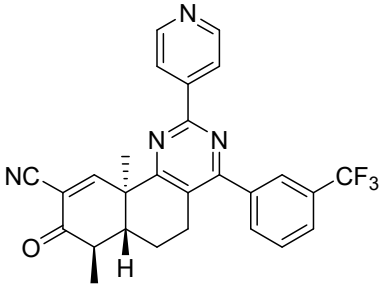
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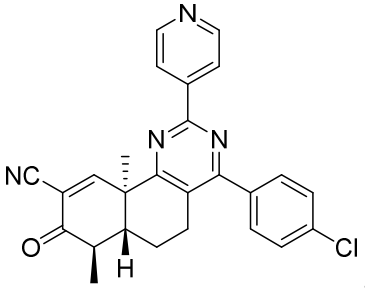
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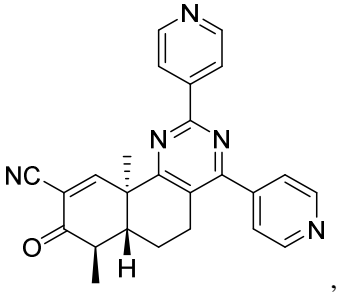
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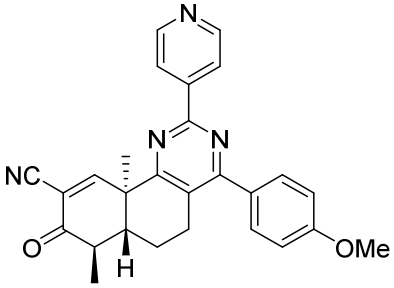
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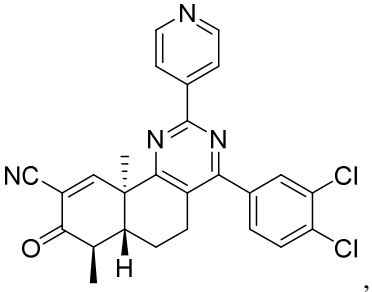
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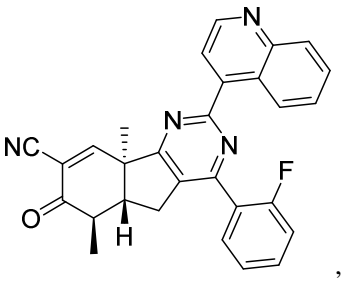
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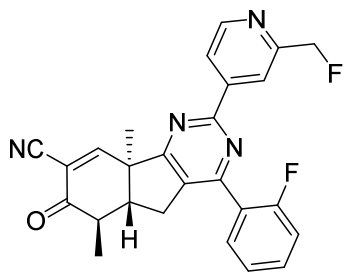
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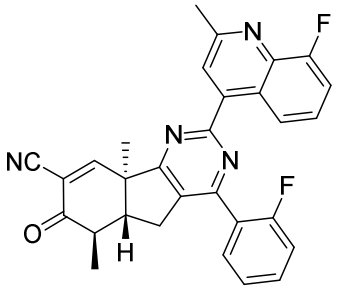
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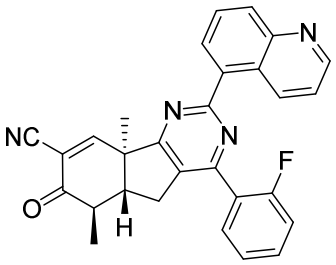
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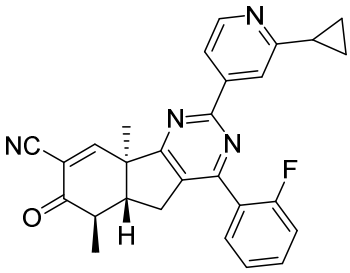
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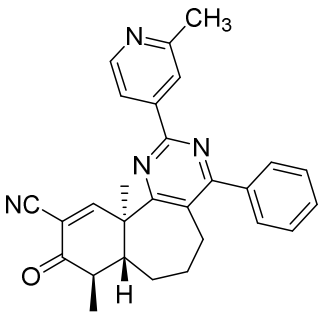
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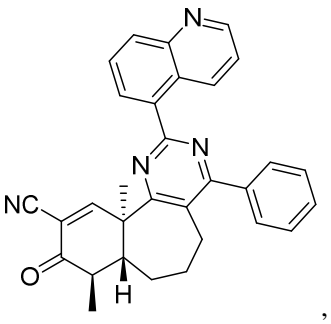
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or a pharmaceutically acceptable salt thereof.

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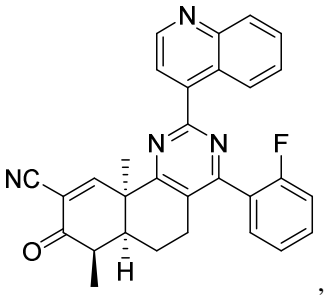

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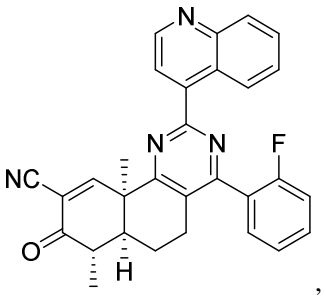

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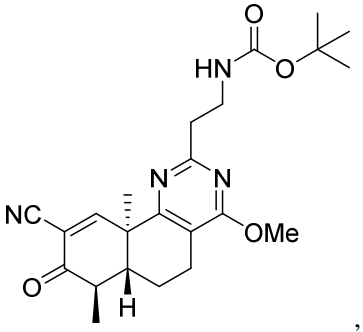

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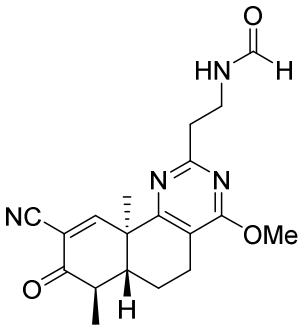

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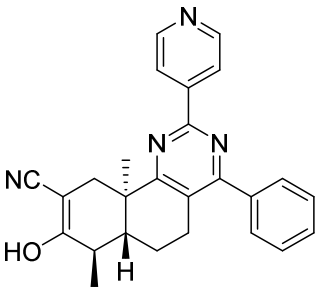

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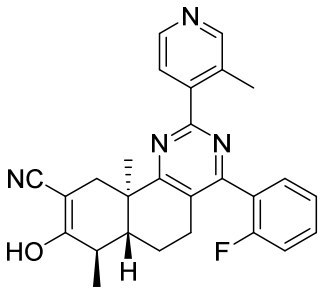

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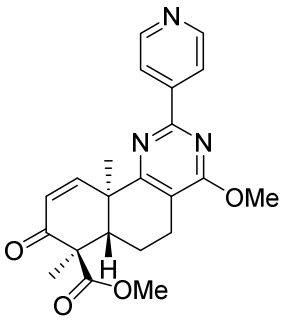

;

or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising:

(A) a compound according to any one of claims 1-21; and

(B) an excipient;

optionally the pharmaceutical composition is formulated for oral administration, administration via injection such as intraarterial administration, intramuscular administration, intraperitoneal administration, or intravenous administration, or topical administration such as topical administration to the skin or to the eye.

23. The pharmaceutical composition of claim 22, wherein the pharmaceutical composition is formulated for oral administration, administration via injection, or topical administration.

24. The pharmaceutical composition of claim 23, wherein the administration via injection is formulated for intraarterial administration, intramuscular administration, intraperitoneal administration, or intravenous administration.

25. The pharmaceutical composition of claim 23, wherein topical administration is topical administration to the skin or to the eye.

26. A compound or composition according to any one of claims 1-25 for use as a medicament.

27. Use of a compound or composition according to any one of claims 1-25 in the manufacture of a medicament for treating or preventing a disease or disorder selected from autoimmune disease, organ rejection, asthma, cancer, a neurological disease, a psychiatric disorder, a neuropsychiatric disorder, chronic pain syndrome, an inflammatory condition, a retinal disorder, or a cardiovascular diseases in a patient in need thereof.