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(54) Title: INHIBITORS OF POLY(ADP-RIBOSE)POLYMERASE

(57) Abrégé/Abstract:

Inhibitors of poly(ADP-ribose)polymerase, ways to make them and methods of treating patients using them are disclosed.

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(54) Title: INHIBITORS OF POLY(ADP-RIBOSE)POLYMERASE

(57) Abstract: Inhibitors of poly(ADP-ribose)polymerase, ways to make them and methods of treating patients using them are disclosed.



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INHIBITORS OF POLY(ADP-RIBOSE)POLYMERASE

FIELD OF THE INVENTION

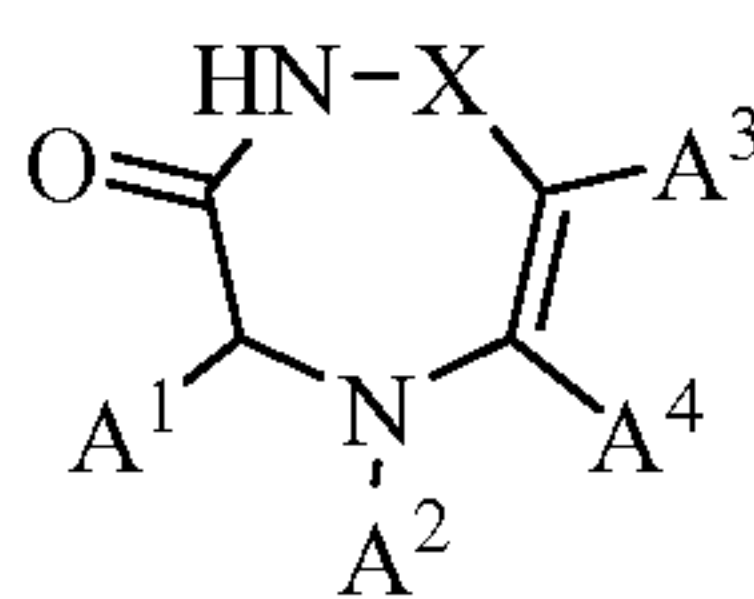
This invention relates to inhibitors of poly(ADP-ribose)polymerase, ways to make
 5 them and methods of treating patients using them.

BACKGROUND OF THE INVENTION

Poly(ADP-ribose)polymerase (PARP) is essential for facilitating DNA repair, controlling RNA transcription, mediating cell death and regulating immune response.
 10 This activity makes PARP inhibitors targets for a number of disorders. PARP inhibitors have shown utility for treating diseases such as ischemia reperfusion injury, inflammatory disease, retroviral infections, ischemia reperfusion injury, myocardial infarction, stroke and other neural trauma, organ transplantation, reperfusion of the eye, kidney, gut and skeletal muscle, arthritis, gout, inflammatory bowel disease, CNS inflammation such as
 15 MS and allergic encephalitis, sepsis, septic shock, hemorrhagic shock, pulmonary fibrosis, and uveitis, diabetes and Parkinsons disease, liver toxicity following acetaminophen overdose, cardiac and kidney toxicities from doxorubicin and platinum-based antineoplastic agents and skin damage secondary to sulfur mustards. PARP inhibitors have also been shown to potentiate radiation and chemotherapy by increasing
 20 cell death of cancer cells, limiting tumor growth, decreasing metastasis, and prolonging the survival of tumor-bearing animals. There is therefore a need in the therapeutic arts for PARP inhibitors.

SUMMARY OF THE INVENTION

25 One embodiment of this invention, therefore, pertains to compounds that inhibit the activity of poly(ADP-ribose) polymerase and have formula I



(I),

30 or a salt thereof, wherein

X is a bond or CH₂;

A¹ and A², together with the atoms to which they are attached, are pyrrole, imidazole, piperidine, or pyrrolidine;

5

A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹,
 10 NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I;

R¹ is R², R³, R⁴ or R⁵;

R² is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 15

R³ is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 20

R⁵ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R⁶, C(O)OH, NH₂, NHR⁶, N(R⁶)₂, C(O)R⁶, C(O)NH₂, C(O)NHR⁶, C(O)N(R⁶)₂, NHC(O)R⁶, NR⁶C(O)R⁶, NR⁶S(O)₂R⁶, F, Cl, Br or I;
 25

R⁶ is R⁷, R⁸, R⁹ or R¹⁰;

R⁷ is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
 30

R⁸ is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

5

R^{10} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, NH_2 , NHR^{11} , $N(R^{11})_2$, $C(O)R^{11}$, $C(O)OR^{11}$, $C(O)NH_2$, $C(O)NHR^{11}$, $C(O)N(R^{11})_2$, $NHC(O)R^{11}$, $NR^{11}C(O)R^{11}$, F, Cl, Br or I;

10

R^{11} is R^{12} , R^{13} , R^{14} or R^{14A} ;

R^{12} is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

15

R^{13} is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20

R^{14A} is alkyl, alkenyl, or alkynyl;

25

wherein the moieties represented by A^1 and A^2 and A^3 and A^4 and the moieties represented by R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{12} , R^{13} and R^{14} are independently unsubstituted or further unsubstituted or independently substituted or further substituted with R^{15} , OR^{15} , SR^{15} , $S(O)R^{15}$, SO_2R^{15} , NH_2 , NHR^{15} , $N(R^{15})_2$, $C(O)R^{15}$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHSO_2R^{15}$, $NR^{15}SO_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, SO_2NH_2 , SO_2NHR^{15} , $SO_2N(R^{15})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)N(R^{15})_2$, OH, (O), $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I;

30

wherein R^{15} is R^{16} , R^{17} , R^{18} or R^{19} ;

R^{16} is phenyl which is unfused or fused with benzene;

R^{17} is heteroaryl which is unfused or fused with benzene;

5

R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene;

10 R^{19} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{20} , $C(O)OH$, NH_2 , NHR^{20} or $N(R^{20})_2$, $C(O)R^{20}$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{20}C(O)R^{20}$, F, Cl, Br or I;

R^{20} is R^{21} or R^{21A} ;

15 R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

20 R^{21A} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{22} , $C(O)OH$, NH_2 , NHR^{22} or $N(R^{22})_2$, $C(O)R^{22}$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, F, Cl, Br or I;

R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

25 wherein the moieties represented by R^{16} , R^{17} , R^{18} , R^{21} , and R^{22} are independently unsubstituted or further unsubstituted or independently substituted or further substituted with R^{23} , OR^{23} , SR^{23} , $S(O)R^{23}$, SO_2R^{23} , NH_2 , NHR^{23} , $N(R^{23})_2$, $C(O)R^{23}$, $C(O)NH_2$, $C(O)NHR^{23}$, $C(O)N(R^{23})_2$, $NHC(O)R^{23}$, $NR^{23}C(O)R^{23}$, $NHSO_2R^{23}$, $NR^{23}SO_2R^{23}$, $NHC(O)OR^{23}$, $NR^{23}C(O)OR^{23}$, SO_2NH_2 , SO_2NHR^{23} , $SO_2N(R^{23})_2$, $NHC(O)NH_2$,
30 $NHC(O)NHR^{23}$, $NHC(O)N(R^{23})_2$, $NR^{23}C(O)N(R^{23})_2$, OH, (O), $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I;

wherein R^{23} is R^{24} , R^{25} , R^{26} or R^{27} ;

R^{24} is phenyl which is unfused or fused with benzene;

R^{25} is heteroaryl which is unfused or fused with benzene;

5 R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene;

R^{27} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{28} , $C(O)OH$, NH_2 , NHR^{28} or $N(R^{28})_2$, $C(O)R^{28}$,
10 $C(O)NH_2$, $C(O)NHR^{28}$, $C(O)N(R^{28})_2$, $NHC(O)R^{28}$, $NR^{28}C(O)R^{28}$, F, Cl, Br or I;

R^{28} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or R^{29} ;

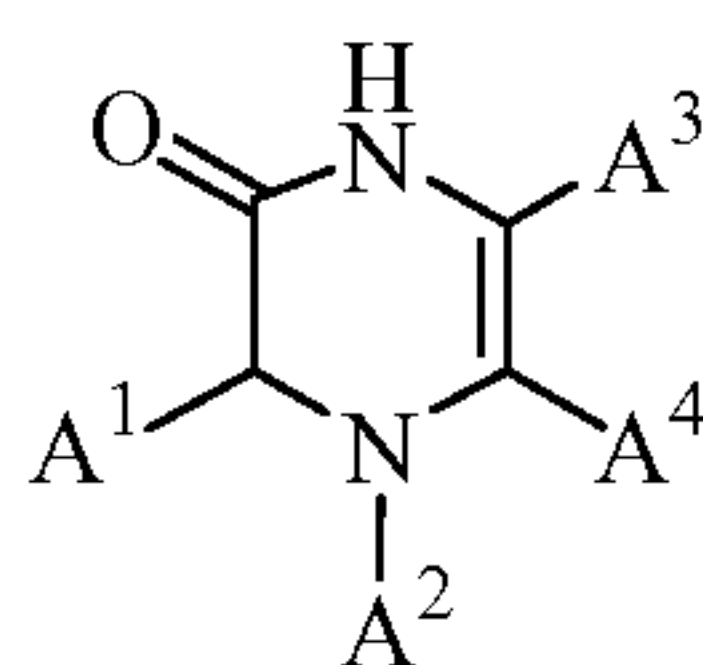
15 R^{29} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{30} , $C(O)OH$, NH_2 , NHR^{30} or $N(R^{30})_2$, $C(O)R^{30}$, $C(O)NH_2$, $C(O)NHR^{30}$, $C(O)N(R^{30})_2$, $NHC(O)R^{30}$, $NR^{30}C(O)R^{30}$, F, Cl, Br or I; and

R^{30} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or
20 heterocycloalkenyl.

 Still another embodiment comprises pharmaceutical compositions comprising a compound having formula I and an excipient.

25 Still another embodiment comprises methods of inhibiting PARP in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

 Still another embodiment comprises methods of treating cancer in a mammal
30 comprising administering thereto a therapeutically acceptable amount of a compound having formula I



(I),

or a salt thereof, wherein

5 A¹ and A², together with the atoms to which they are attached, are pyrrole;

 A³ and A⁴, together with the atoms to which they are attached, are benzene which
is substituted with R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂,
C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹¹C(O)R¹¹, NHSO₂R¹¹, NR¹¹SO₂R¹¹,
10 NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂,
NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I;

 R¹ is R², R³, R⁴ or R⁵;

15 R² is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane,
cycloalkene, heterocycloalkane or heterocycloalkene;

 R³ is heteroarene which is unfused or fused with benzene, heteroarene,
cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20

 R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of
which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene,
heterocycloalkane or heterocycloalkene;

25 R⁵ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with
one or two of independently selected R⁶, C(O)OH, NH₂, NHR⁶ or N(R⁶)₂, C(O)R⁶,
C(O)NH₂, C(O)NHR⁶, C(O)N(R⁶)₂, NHC(O)R⁶, NR⁶C(O)R⁶, F, Cl, Br or I;

 R⁶ is R⁷, R⁸, R⁹ or R¹⁰;

30

R^7 is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^8 is heteroarene which is unfused or fused with benzene, heteroarene,
5 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
10

R^{10} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, NH_2 , NHR^{11} or $N(R^{11})_2$, $C(O)R^{11}$, $C(O)NH_2$, $C(O)NHR^{11}$, $C(O)N(R^{11})_2$, $NHC(O)R^{11}$, $NR^{11}C(O)R^{11}$, F, Cl, Br or I;

15 R^{11} is R^{12} , R^{13} or R^{14} ;

R^{12} is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20 R^{13} is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene,
25 heterocycloalkane or heterocycloalkene;

wherein the moieties represented by A^1 and A^2 and A^3 and A^4 and the moieties represented by R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{12} , R^{13} or R^{14} are independently unsubstituted or further unsubstituted or independently substituted or further substituted with R^{20} , OR^{20} ,
30 SR^{20} , $S(O)R^{20}$, SO_2R^{20} , NH_2 , NHR^{20} , $N(R^{20})_2$, $C(O)R^{20}$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{10}C(O)R^{20}$, $NHSO_2R^{20}$, $NR^{20}SO_2R^{20}$, $NHC(O)OR^{20}$, $NR^{20}C(O)OR^{20}$, SO_2NH_2 , SO_2NHR^{20} , $SO_2N(R^{20})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{20}$, $NHC(O)N(R^{20})_2$, $NR^{20}C(O)N(R^{20})_2$, OH, (O), $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I;

wherein R^{20} is R^{21} , R^{22} , R^{23} or R^{24} ;

R^{21} is phenyl which is unfused or fused with benzene;

5

R^{22} is heteroaryl which is unfused or fused with benzene;

R^{23} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene;

10

R^{24} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{25} , $C(O)OH$, NH_2 , NHR^{25} or $N(R^{25})_2$, $C(O)R^{25}$, $C(O)NH_2$, $C(O)NHR^{25}$, $C(O)N(R^{25})_2$, $NHC(O)R^{25}$, $NR^{25}C(O)R^{25}$, F, Cl, Br or I;

15

R^{25} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or R^{26} ;

R^{26} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{27} , $C(O)OH$, NH_2 , NHR^{27} or $N(R^{27})_2$, $C(O)R^{27}$,

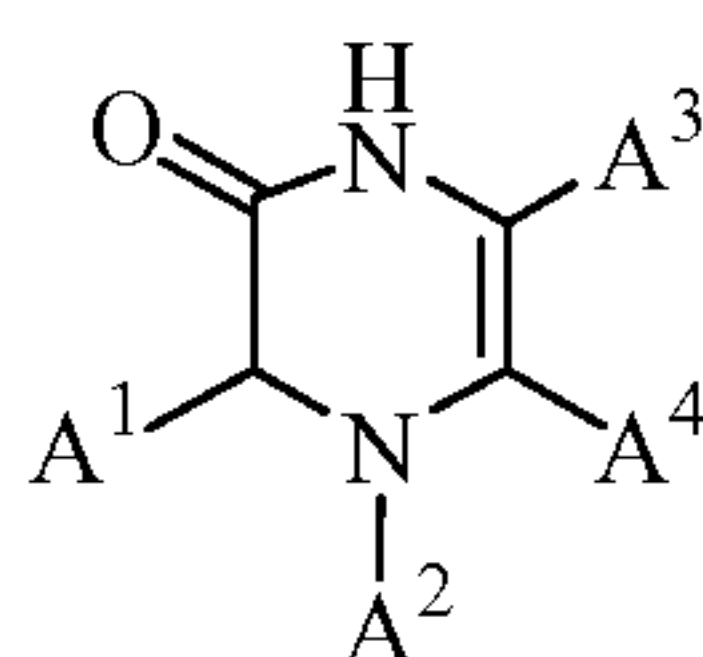
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$C(O)NH_2$, $C(O)NHR^{27}$, $C(O)N(R^{27})_2$, $NHC(O)R^{27}$, $NR^{27}C(O)R^{27}$, F, Cl, Br or I;

R^{27} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl.

25

Still another embodiment comprises methods for decreasing tumor volume in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula IA



(IA),

30

and salts thereof, wherein

A¹ and A², together with the atoms to which they are attached, are pyrrole;

A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂,
 5 C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹¹C(O)R¹¹, NHSO₂R¹¹, NR¹¹SO₂R¹¹,
 NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂,
 NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I;

10 R¹ is R², R³, R⁴ or R⁵;

R² is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

15 R³ is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20 R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R⁵ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R⁶, C(O)OH, NH₂, NHR⁶ or N(R⁶)₂, C(O)R⁶, C(O)NH₂, C(O)NHR⁶, C(O)N(R⁶)₂, NHC(O)R⁶, NR⁶C(O)R⁶, F, Cl, Br or I;

25 R⁶ is R⁷, R⁸, R⁹ or R¹⁰;

R⁷ is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

30 R⁸ is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

5 R^{10} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, NH_2 , NHR^{11} or $N(R^{11})_2$, $C(O)R^{11}$, $C(O)NH_2$, $C(O)NHR^{11}$, $C(O)N(R^{11})_2$, $NHC(O)R^{11}$, $NR^{11}C(O)R^{11}$, F, Cl, Br or I;

R^{11} is R^{12} , R^{13} or R^{14} ;

10

R^{12} is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

15 R^{13} is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20

wherein the moieties represented by A^1 and A^2 and A^3 and A^4 and the moieties represented by R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{12} , R^{13} or R^{14} are independently unsubstituted or further unsubstituted or independently substituted or further substituted with R^{20} , OR^{20} , SR^{20} , $S(O)R^{20}$, SO_2R^{20} , NH_2 , NHR^{20} , $N(R^{20})_2$, $C(O)R^{20}$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{10}C(O)R^{20}$, $NHSO_2R^{20}$, $NR^{20}SO_2R^{20}$, $NHC(O)OR^{20}$, $NR^{20}C(O)OR^{20}$, SO_2NH_2 , SO_2NHR^{20} , $SO_2N(R^{20})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{20}$, $NHC(O)N(R^{20})_2$, $NR^{20}C(O)N(R^{20})_2$, OH, (O), $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I;

30 wherein R^{20} is R^{21} , R^{22} , R^{23} or R^{24} ;

R^{21} is phenyl which is unfused or fused with benzene;

R^{22} is heteroaryl which is unfused or fused with benzene;

R^{23} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene;

5 R^{24} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{25} , $C(O)OH$, NH_2 , NHR^{25} or $N(R^{25})_2$, $C(O)R^{25}$, $C(O)NH_2$, $C(O)NHR^{25}$, $C(O)N(R^{25})_2$, $NHC(O)R^{25}$, $NR^{25}C(O)R^{25}$, F, Cl, Br or I;

10 R^{25} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or R^{26} ;

R^{26} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{27} , $C(O)OH$, NH_2 , NHR^{27} or $N(R^{27})_2$, $C(O)R^{27}$, $C(O)NH_2$, $C(O)NHR^{27}$, $C(O)N(R^{27})_2$, $NHC(O)R^{27}$, $NR^{27}C(O)R^{27}$, F, Cl, Br or I; and
15

R^{27} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl.

Still another embodiment comprises a method of treating leukemia, colon cancer,
20 glioblastomas, lymphomas, melanomas, carcinomas of the breast or cervical carcinomas in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

Still another embodiment comprises methods for potentiation of cytotoxic cancer
25 therapy in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

Still another embodiment comprises methods for potentiation of radiation therapy
in a mammal comprising administering thereto a therapeutically acceptable amount of a
30 compound having formula I.

Still another embodiment comprises methods of treating ischemia reperfusion injury associated with myocardial infarction, stroke, neural trauma or organ

transplantation in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

5 Still another embodiment comprises methods of treating reperfusion of the eye, kidney, gut or skeletal muscle in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

10 Still another embodiment comprises methods of treating arthritis, gout, inflammatory bowel disease, CNS inflammation, multiple sclerosis, allergic encephalitis, sepsis, septic shock, hemorrhagic shock, pulmonary fibrosis or uveitis in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

15 Still another embodiment comprises a method of treating rheumatoid arthritis or septic shock in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

20 Still another embodiment comprises methods of treating diabetes or Parkinsons disease in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

25 Still another embodiment comprises methods of treating hypoglycemia in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

Still another embodiment comprises methods of treating retroviral infection in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

30 Still another embodiment comprises methods of treating liver toxicity following acetaminophen overdose in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

Still another embodiment comprises a method of treating cardiac or kidney toxicities from doxorubicin or platinum based antineoplastic agents in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

5

Still another embodiment comprises methods of treating skin damage secondary to sulfur mustards in a mammal comprising administering thereto a therapeutically acceptable amount of a compound having formula I.

10

Still another embodiment comprises the compounds:

- 7-((cyclohexylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7-(((cyclohexylmethyl)amino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7-((cyclobutylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7-((cyclopentylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 15 7-((cyclopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7-(piperidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7-(pyrrolidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-((cyclohexylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-(((cyclohexylmethyl)amino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 20 7-((isopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7-((benzylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-((cyclopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-((isopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-(((2-phenylethyl)amino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 25 8-(pyrrolidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-((cyclobutylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-(morpholin-4-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-((cyclopentylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 8-(piperidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 30 8-((benzylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7-(pyrrolidin-1-ylmethyl)imidazo[1,2-a]quinoxalin-4(5H)-one,
- 7-(piperidin-1-ylmethyl)imidazo[1,2-a]quinoxalin-4(5H)-one,
- 7-((dimethylamino)methyl)imidazo[1,2-a]quinoxalin-4(5H)-one,
- 7-(((cyclohexylmethyl)amino)methyl)imidazo[1,2-a]quinoxalin-4(5H)-one,

- 7-(morpholin-4-ylmethyl)imidazo[1,2-a]quinoxalin-4(5H)-one,
 8-((dimethylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
 8-(pyrrolidin-1-ylmethyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
 8-((isopropylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
 5 8-((4-methylpiperazin-1-yl)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
 8-(((2-ethoxyethyl)(methyl)amino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
 8-(((cyclohexylmethyl)amino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-
 10 4-one,
 8-((benzylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
 8-((cyclopentylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
 3-(pyrrolidin-1-ylmethyl)-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 3-[(dimethylamino)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 15 3-[(cyclohexylamino)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 3-(piperidin-1-ylmethyl)-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 3-[(isopropylamino)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 3-{[ethyl(methyl)amino]methyl}-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-
 20 one,
 3-{[cyclohexyl(methyl)amino]methyl}-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 3-{[isopropyl(methyl)amino]methyl}-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 25 3-[(4-methylpiperazin-1-yl)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one,
 7-(pyrrolidin-1-ylmethyl)-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,
 7-[(dimethylamino)methyl]-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,
 7-(piperidin-1-ylmethyl)-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,
 30 7-{[ethyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,
 7-{[cyclohexyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,
 7-[(4-methylpiperazin-1-yl)methyl]-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,

- 7- {[benzyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7- {[isopropyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 5 N-cyclopropyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-8-yl)methyl]methanesulfonamide
- 7-[(2-oxopyrrolidin-1-yl)methyl]pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- N-cyclobutyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-8-yl)methyl]ethanesulfonamide,
- 10 N-isopropyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-8-yl)methyl]benzenesulfonamide,
- N-cyclobutyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]acetamide,
- N-cyclopropyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]methanesulfonamide,
- 15 8-(piperidin-1-ylmethyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
- 8-[(cyclohexylamino)methyl]-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one,
- methyl N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]glycinate,
- N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]glycine,
- 4-oxo-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
- 20 7- {[2-(pyrrolidin-1-ylethyl)amino]methyl}pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- N-(3-morpholin-4-ylpropyl)-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
- N-(2-morpholino-2-oxoethyl)-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
- 7- {[2-(dimethylamino)ethyl]amino}methylpyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 25 N-[3-(4-methylpiperazin-1-yl)propyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
- 7- {[3-(morpholin-4-ylpropyl)amino]methyl}pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- N-[2-(dimethylamino)ethyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
- 7- {[3-(piperidin-1-ylpropyl)amino]methyl}pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 30 4-oxo-N-(3-piperidin-1-ylpropyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
- 7- {[2-(piperidin-1-ylethyl)amino]methyl}pyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 7- {[4-(dimethylamino)cyclohexyl]amino}methylpyrrolo[1,2-a]quinoxalin-4(5H)-one,
- 4-oxo-N-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,

- N-[4-(dimethylamino)cyclohexyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 4-oxo-N-[3-(piperidin-1-ylsulfonyl)phenyl]-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 5 7-((2-oxo-2-(pyrrolidin-1-yl)ethylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
 4-oxo-N-(pyridin-4-ylmethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 4-oxo-N-(2-thiomorpholin-4-ylethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 N,N-dimethyl-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 10 N-(1-ethylpiperidin-3-yl)-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 4-oxo-N-(4-phenylbutyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 7-(pyrrolidin-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
 N-[4-(4-benzylpiperazin-1-yl)phenyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 15 4-oxo-N-1,3-thiazol-2-yl-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide,
 7-(piperidin-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
 7-[(4-aminopiperidin-1-yl)methyl]pyrrolo[1,2-a]quinoxalin-4(5H)-one,
 7-[(4-aminopiperidin-1-yl)carbonyl]pyrrolo[1,2-a]quinoxalin-4(5H)-one,
 7-(1,4-diazepan-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
 20 6-(pyrrolidin-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one,
 and therapeutically salts, prodrugs, esters, amides, salts of prodrugs, salts of esters
 and salts of amides thereof.

DETAILED DESCRIPTION OF THE INVENTION

- 25 Variable moieties of compounds herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

- It is meant to be understood that proper valences are maintained for all combinations herein, that monovalent moieties having more than one atom are attached
 30 through their left ends.

It is also meant to be understood that a specific embodiment of a variable moiety may be the same or different as another specific embodiment having the same identifier.

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are: "DMF" for N,N-dimethylformamide, "DMSO" for dimethylsulfoxide, "HATU" for O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, "TFA" for trifluoroacetic acid, "THF" for tetrahydrofuran, and "Pd/C" for palladium/carbon.

The term "alkenyl," as used herein, means monovalent, straight or branched chain hydrocarbon moieties having one or more than one carbon-carbon double bonds, such as C₂-alkenyl, C₃-alkenyl, C₄-alkenyl, C₅-alkenyl, C₆-alkenyl and the like.

10

The term "alkyl," as used herein, means monovalent, saturated, straight or branched chain hydrocarbon moieties, such as C₁-alkyl, C₂-alkyl, C₃-alkyl, C₄-alkyl, C₅-alkyl, C₆-alkyl and the like.

The term "alkynyl," as used herein, means monovalent, straight or branched chain hydrocarbon moieties having one or more than one carbon-carbon triple bonds, such as C₂-alkynyl, C₃-alkynyl, C₄-alkynyl, C₅-alkynyl, C₆-alkynyl and the like.

The term "cycloalkane," as used herein, means saturated cyclic or bicyclic hydrocarbon moieties, such as C₄-cycloalkane, C₅-cycloalkane, C₆-cycloalkane, C₇-cycloalkane, C₈-cycloalkane, C₉-cycloalkane, C₁₀-cycloalkane, C₁₁-cycloalkane, C₁₂-cycloalkane and the like.

The term "cycloalkyl," as used herein, means monovalent, saturated cyclic and bicyclic hydrocarbon moieties, such as C₃-cycloalkyl, C₄-cycloalkyl, C₅-cycloalkyl, C₆-cycloalkyl, C₇-cycloalkyl, C₈-cycloalkyl, C₉-cycloalkyl, C₁₀-cycloalkyl, C₁₁-cycloalkyl, C₁₂-cycloalkyl and the like.

The term "cycloalkene," as used herein, means cyclic and bicyclic hydrocarbon moieties having one or more than one carbon-carbon double bonds, such as C₅-cycloalkene, C₆-cycloalkene, C₇-cycloalkene, C₈-cycloalkene, C₉-cycloalkene, C₁₀-cycloalkene, C₁₁-cycloalkene, C₁₂-cycloalkene and the like.

30

The term “cycloalkenyl,” as used herein, means monovalent, cyclic hydrocarbon moieties having one or more than one carbon-carbon double bonds, such as C₄-cycloalkenyl, C₅-cycloalkenyl, C₆-cycloalkenyl, C₇-cycloalkenyl, C₈-cycloalkenyl, C₉-cycloalkenyl, C₁₀-cycloalkenyl, C₁₁-cycloalkenyl, C₁₂-cycloalkenyl and the like.

5

The term “heteroarene,” as used herein, means furan, imidazole, isothiazole, isoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, 1,3,4-thiadiazole, thiophene, triazine and 1,2,3-triazole.

10

The term “heteroaryl,” as used herein, means furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, 1,2,3-thiadiazoyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thiophenyl, triazinyl and 1,2,3-triazolyl.

15

The term “heterocycloalkane,” as used herein, means cycloalkane having one or two or three CH₂ moieties replaced with independently selected O, S, S(O), SO₂ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkane having one or two or three CH₂ moieties unreplaced or replaced with independently selected O, S, S(O), SO₂ or NH and one or two CH moieties replaced with N.

20

The term “heterocycloalkene,” as used herein, means cycloalkene having one or two or three CH₂ moieties replaced with independently selected O, S, S(O), SO₂ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkene having one or two or three CH₂ moieties unreplaced or replaced with independently selected O, S, S(O), SO₂ or NH and one or two CH moieties replaced with N.

25

The term “heterocycloalkyl,” as used herein, means cycloalkyl having one or two or three CH₂ moieties replaced with independently selected O, S, S(O), SO₂ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkyl having one or two or three CH₂ moieties unreplaced or replaced with independently selected O, S, S(O), SO₂ or NH and one or two CH moieties replaced with N.

30

The term "heterocycloalkenyl," as used herein, means cycloalkenyl having one or two or three CH₂ moieties replaced with independently selected O, S, S(O), SO₂ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkenyl having one or two or three CH₂ moieties unreplaced or replaced with independently
5 selected O, S, S(O), SO₂ or NH and one or two CH moieties replaced with N.

The term "cyclic moiety," as used herein, means benzene, cycloalkane, cycloalkyl, cycloalkene, cycloalkenyl, heteroarene, heteroaryl, heterocycloalkane, heterocycloalkyl, heterocycloalkene, heterocycloalkenyl and phenyl.
10

Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, wherein the terms "R" and "S" are as defined in Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those atoms. Atoms
15 having excess of one configuration over the other are assigned the configuration in excess, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention is meant to embrace racemic mixtures, relative and absolute diastereoisomers and the compounds thereof.

20 Compounds of this invention may also contain carbon-carbon double bonds or carbon-nitrogen double bonds in the Z or E configuration, in which the term "Z" represents the larger two substituents on the same side of a carbon-carbon or carbon-nitrogen double bond and the term "E" represents the larger two substituents on
25 opposite sides of a carbon-carbon or carbon-nitrogen double bond. The compounds of this invention may also exist as a mixture of "Z" and "E" isomers.

Compounds of this invention containing NH, C(O)H, C(O)OH, C(O)NH₂, OH or SH moieties may have attached thereto prodrug-forming moieties. The prodrug-forming
30 moieties are removed by metabolic processes and release the compounds having the freed NH, C(O)H, C(O)OH, C(O)NH₂, OH or SH in vivo. Prodrugs are useful for adjusting such pharmacokinetic properties of the compounds as solubility and/or hydrophobicity, absorption in the gastrointestinal tract, bioavailability, tissue penetration, and rate of clearance.

Metabolites of compounds having Formula I, produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases caused or exacerbated by unregulated or overexpressed poly(ADP-ribose)polymerase.

5

Certain precursor compounds of compounds having Formula I may be metabolized in vitro or in vivo to form compounds having Formula I and may thereby also have utility for treating diseases caused or exacerbated by unregulated or overexpressed poly(ADP-ribose)polymerase.

10

Compounds having Formula I may exist as acid addition salts, basic addition salts or zwitterions. Salts of compounds having Formula I are prepared during their isolation or following their purification. Acid addition salts are those derived from the reaction of a compound having Formula I with acid. Accordingly, salts including the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate and undecanoate salts of the compounds having Formula I are meant to be embraced by this invention. Basic addition salts of compounds are those derived from the reaction of the compounds having Formula I with the bicarbonate, carbonate, hydroxide, or phosphate of cations such as lithium, sodium, potassium, calcium and magnesium.

25

Compounds having Formula I may be administered, for example, buccally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally, intrasternally, intravenously, subcutaneously), rectally, topically, transdermally and vaginally.

30

Therapeutically effective amounts of a compound having Formula I depend on recipient of treatment, disease treated and severity thereof, composition comprising it, time of administration, route of administration, duration of treatment, potency, rate of

clearance and whether or not another drug is co-administered. The amount of a compound having Formula I used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.001 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

5

Compounds having Formula I may be administered with or without an excipient. Excipients include, for example, encapsulators and additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

Compounds having Formula I may be radiolabeled with a radioactive isotope such as carbon (i.e. ^{13}C), hydrogen (i.e. ^3H), nitrogen (i.e. ^{15}N), phosphorus (i.e. ^{32}P), sulfur (i.e. ^{35}S), iodide (i.e. ^{125}I) and the like. Radioactive isotopes may be incorporated into the compounds having Formula I by reacting the same and a radioactive derivitizing agent or by incorporating a radiolabeled intermediate into their syntheses. The radiolabeled compounds of Formula I are useful for both prognostic and diagnostic applications and for in vivo and in vitro imaging.

20

Compounds having Formula I may be incorporated into devices such as, but not limited to, arterio-venous grafts, billiary stents, by-pass grafts, catheters, central nervous system shunts, coronary stents, drug delivery balloons, peripheral stents and ureteural stents, each of which may be used in areas such as, but not limited to, the vasculature for introduction of a compound having Formula I into selected tissues or organs in the body. One measure of the effectiveness of compounds having Formula I is reduction or elimination of device-associated thrombi and complications associated therewith.

Compounds having Formula I can used as a radiosensitizers which enhance the efficacy of radiotherapy. Examples of radiotherapy include, but are not limited to, external beam radiotherapy, teletherapy, brachtherapy and sealed and unsealed source radiotherapy.

30

Excipients for preparation of compositions comprising a compound having Formula I to be administered orally include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-

5 povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium

10 carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water and mixtures thereof. Excipients for preparation of compositions comprising a compound having Formula I to be administered ophthalmically or orally include, for example, 1,3-butylene glycol, castor oil, corn oil,

15 cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound having Formula I to be administered osmotically include, for example, chlorofluoro-hydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of

20 compositions comprising a compound having Formula I to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions comprising a compound having

25 Formula I to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

Compounds having formula I are also expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics,

30 antiproliferatives, aurora kinase inhibitors, Bcr-Abl kinase inhibitors, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors inhibitors, hormonal therapies, immunologicals, intercalating antibiotics, kinase inhibitors,

mammalian target of rapomycin inhibitors, mitogen-activated extracellular signal-regulated kinase inhibitors, non-steroidal anti-inflammatory drugs (NSAID's), platinum chemotherapeutics, polo-like kinase inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids,
 5 topoisomerase inhibitors and the like.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, Cloretazine™ (VNP 40101M), cyclophosphamide, decarbazine, estramustine,
 10 fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, treosulfan, trofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase
 15 (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

20

Aurora kinase inhibitors include AZD-1152, MLN-8054, VX-680 and the like.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (imatinib) and the like.

25

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

30 COX-2 inhibitors include ABT-963, ARCOXIA® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX™ (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole, MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX® (rofecoxib) and the like.

EGFR inhibitors include ABX-EGF, anti-EGFr immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX[®] (cetuximab), HR3, IgA antibodies, IRESSA[®] (gefitinib), TARCEVA[®] (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB[®] (lapatinib)
 5 and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), Herceptin[®] (trastuzumab), TYKERB[®] (lapatinib), OMNITARG[®] (2C4, petuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine),
 10 APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecific antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.
 15

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB[®], NCS-683664, PU24FCl, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

20 MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus and the like.
 25

Non-steroidal anti-inflammatory drugs include AMIGESIC[®] (salsalate), DOLOBID[®] (diflunisal), MOTRIN[®] (ibuprofen), ORUDIS[®] (ketoprofen), RELAFEN[®] (nabumetone), FELDENE[®] (piroxicam) ibuprofen cream, ALEVE[®] and NAPROSYN[®] (naproxen), VOLTAREN[®] (diclofenac), INDOCIN[®] (indomethacin), CLINORIL[®]
 30 (sulindac), TOLECTIN[®] (tolmetin), LODINE[®] (etodolac), TORADOL[®] (ketorolac), DAYPRO[®] (oxaprozin) and the like.

PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

Platinum chemotherapeutics include cisplatin, ELOXATIN[®] (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN[®] (carboplatin), satraplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

5

Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

10 VEGFR inhibitors include AVASTIN[®] (bevacizumab), ABT-869, AEE-788, ANGIOZYME[™], axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, Macugen (pegaptamib), NEXAVAR[®] (sorafenib, BAY43-9006), pazopanib (GW-786034), (PTK-787, ZK-222584), SUTENT[®] (sunitinib, SU-11248), VEGF trap, vatalanib, ZACTIMA[™] (vandetanib, ZD-6474) and the like.

15 Antimetabolites include ALIMTA[®] (premetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA[®] (capecitabine), carmofur, LEUSTAT[®] (cladribine), clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR, enocitabine, ethnylcytidine, fludarabine, hydroxyurea, 5-fluorouracil (5-FU) alone or in combination with leucovorin, GEMZAR[®] (gemcitabine),
20 hydroxyurea, ALKERAN[®] (melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

25 Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE[®] (bleomycin), daunorubicin, CAELYX[®] or MYOCET[®] (doxorubicin), elsamitrucin, epirbucin, glarbuicin, ZAVEDOS[®] (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR[®] (valrubicin), zinostatin and the like.

30

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR[®] (irinotecan hydrochloride), camptothecin, CARDIOXANE[®] (dexrazoxine), diflomotecan, edotecarin, ELLENCE[®] or PHARMORUBICIN[®] (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin,

gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbutin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

Antibodies include AVASTIN[®] (bevacizumab), CD40-specific antibodies, chTNT-
 5 1/B, denosumab, ERBITUX[®] (cetuximab), HUMAX-CD4[®] (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX[®] (edrecolomab), RENCAREX[®] (WX G250), RITUXAN[®] (rituximab), ticilimumab, trastuzimab and the like.

Hormonal therapies include ARIMIDEX[®] (anastrozole), AROMASIN[®]
 10 (exemestane), arzoxifene, CASODEX[®] (bicalutamide), CETROTIDE[®] (cetorelix), degarelix, deslorelin, DESOPAN[®] (trilostane), dexamethasone, DROGENIL[®], (flutamide), EVISTA[®] (raloxifene), fadrozole, FARESTON[®] (toremifene), FASLODEX[®] (fulvestrant), FEMARA[®], (letrozole), formestane, glucocorticoids, HECTOROL[®] or RENAGEL[®] (doxercalciferol), lasofoxifene, leuprolide acetate, MEGACE[®] (megesterol),
 15 MIFEPREX[®] (mifepristone), NILANDRON[™] (nilutamide), NOLVADEX[®] (tamoxifen citrate), PLENAXIS[™] (abarelix), predisone, PROPECIA[®] (finasteride), rilostane, SUPREFACT[®] (buserelin), TRELSTAR[®] (luteinizing hormone releasing hormone (LHRH)), vantas, VETORYL[®], (trilostane or modrastane), ZOLADEX[®] (fosrelin, goserelin) and the like.

20

Deltoids and retinoids include seocalcitrol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN[®] (aliretinoin), ATRAGEN[®] (liposomal tretinoin), TARGRETIN[®] (bexarotene), LGD-1550 and the like.

25 Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

Proteasome inhibitors include VELCADE[®] (bortezomib), MG132, NPI-0052, PR-171 and the like.

30

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE[®] (interferon gamma-1b), or interferon gamma-n1, combinations thereof and the like. Other agents include

ALFAFERONE[®] (Interferon alfa), BAM-002, BEROMUN[®] (tasonermin), BEXXAR[®] (tositumomab), CAMPATH[®] (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE[®] (lenograstim), lentinan, leukocyte alpha interferon, imiquimod, MDX-010, melanoma vaccine, mitumomab, molgramostim, MYLOTARG[™] (gemtuzumab ozogamicin), NEUPOGEN[®] (filgrastim), OncoVAC-CL, OVAREX[®] (oregovomab), pentumomab (Y-muHMFG1), PROVENGE[®] (sipuleucel-T), sargaramostim, sizofiran, teceleukin, THERACYS[®] (BCG Live (Intravesical)), ubenimex, VIRULIZIN[®] (biological response modifier obtained from bovine bile), Z-100, WF-10, PROLEUKIN[®] (aldesleukin), ZADAXIN[®] (thymalfasin), ZENAPAX[®] (daclizumab), ZEVALIN[®] (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity and include krestin, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C), cytosine arabinoside, doxifluridine, FLUDARA[®] (fludarabine), 5-FU (5-fluorouracil), floxuridine, GEMZAR[®] (gemcitabine), TOMUDEX[®] (ratitrexed), TROXATYL[™] (triacetyluridine troxacitabine) and the like.

20

Purine analogs include LANVIS[®] (thioguanine) and PURI-NETHOL[®] (mercaptopurine).

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE[®] (docetaxel), PNU100940 (109881), patupilone, XRP-9881, vinflunine, ZK-EPO and the like.

Compounds of the present invention are also intended to be used as a radiosensitizer that enhances the efficacy of radiotherapy. Examples of radiotherapy include, but are not limited to, external beam radiotherapy, teletherapy, brachtherapy and sealed and unsealed source radiotherapy.

Additionally, compounds having formula I may be combined with other chemoptherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN® (Ad5CMV-p53), ALTOCOR® or MEVACOR® (lovastatin), AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN™ (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotne), AVE-8062, BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CeaVac™ (cancer vaccine), CELEUK® (celmoleukin), CEPLENE® (histamine dihydrochloride), CERVARIX™ (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CyPat™, combrestatin A4P, DAB(389)EGF or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON™ (squalamine lactate), DIMERICINE® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906, GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), gastrimmune, genasense, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon- α , interferon- γ , JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT® (AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), OncoVAX (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OvaRex® MAb (murine monoclonal antibody), paditaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), Taxoprexin® (DHA-paclitaxel), TELCYTA™ (TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFerade™ (adenovector: DNA carrier containing the gene for tumor

necrosis factor- α), TRACLEER[®] or ZAVESCA[®] (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX[®] (arsenic trioxide), VIRULIZIN[®], ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti- α v β 3 antibody), XCYTRIN[®] (motexafin gadolinium), XINLAY[™] (atrasentan), XYOTAX[™] (paclitaxel poliglumex),
 5 YONDELIS[™] (trabectedin), ZD-6126, ZINECARD[®] (dexrazoxane), zometa (zoledronic acid), zorubicin and the like.

It is expected that compounds having formula I would also inhibit growth of cells derived from a pediatric cancer or neoplasm including embryonal rhabdomyosarcoma,
 10 pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoid/rhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitt's lymphoma, pediatric cancers of Ewing's family of tumors such as primitive
 15 neuroectodermal tumors, pediatric diffuse anaplastic Wilms' tumor, pediatric favorable histology Wilms' tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric osteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin
 20 cancer and the like (commonly-owned United States Application Ser No. 10/988,338), Cancer Res., 2000, 60, 6101-10); and autoimmune disorders include, acquired immunodeficiency disease syndrome, autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, thrombocytopenia and the like (Current Allergy and Asthma Reports 2003, 3:378-384; Br. J. Haematol. 2000 Sep; 110(3): 584-90; Blood
 25 2000 Feb 15;95(4):1283-92; and New England Journal of Medicine 2004 Sep; 351(14): 1409-1418).

Inhibition of PARP

Nicotinamide[2,5',8-3H]adenine dinucleotide and streptavidin SPA beads were
 30 purchased from Amersham Biosciences (Buckinghamshire, U.K.). Recombinant Human Poly(ADP-Ribose) Polymerase (PARP), purified from E.coli and 6-Biotin-17-NAD⁺, were purchased from Trevigen (Gaithersburg, MD). NAD⁺, histone, aminobenzamide, 3-amino benzamide and Calf Thymus DNA (dcDNA) were purchased from Sigma (St. Louis, MO). Stem loop oligonucleotide containing MCAT sequence was obtained from

Qiagen (Valencia, CA). The oligos were dissolved to 1 mM in annealing buffer containing 10 mM Tris HCl pH 7.5, 1 mM EDTA, and 50 mM NaCl, incubated for 5 minutes at 95°C, and annealed at 45°C for 45 minutes. Histone H1 (95% electrophoretically pure) was purchased from Roche (Indianapolis, IN). Biotinylated histone H1 was prepared by treating the protein with Sulfo-NHS-LC-Biotin from Pierce (Rockford, IL). The biotinylation reaction was conducted by slowly and intermittently adding 3 equivalents of 10mM Sulfo-NHS-LC-Biotin to 100µM Histone H1 in phosphate-buffered saline, pH 7.5, at 4°C with gentle vortexing over 1 minute followed by subsequent 4°C incubation for 1 hour. Streptavidin coated (FLASHPLATE PLUS ®) microplates were purchased from Perkin Elmer (Waltham, MA).

PARP1 assay was conducted in PARP assay buffer containing 50 mM Tris pH 8.0, 1mM DTT, 4 mM MgCl₂. PARP reactions contained 1.5 µM [³H]-NAD⁺ (1.6uCi/mmol), 200 nM biotinylated histone H1, 200 nM siDNA, and 1 nM PARP enzyme. Auto reactions utilizing SPA bead-based detection were carried out in 100 µL volumes in white 96 well plates. Reactions were initiated by adding 50 µl of 2X NAD⁺ substrate mixture to 50 µL of 2X enzyme mixture containing PARP and DNA. These reactions were terminated by the addition of 150 µL of 1.5 mM benzamide (~1000-fold over its IC₅₀). 170 µL of the stopped reaction mixtures were transferred to streptavidin FLASHPLATE PLUS®, incubated for 1 hour, and counted using a TOPCOUNT® microplate scintillation counter from Perkin Elmer (Waltham, MA). The EC_{50s} for exemplified compounds of this invention are provided in Table 1.

Cellular PARP assay:

C41 cells were treated with a compound of this invention for 30 minutes in 96 well plate. PARP was then activated by damaging DNA with 1 mM H₂O₂ for 10 minutes. The cells were then washed with ice-cold PBS once and fixed with pre-chilled methanol:acetone (7:3) at -20°C for 10 minutes. After air-drying, the plates were rehydrated with PBS and blocked 5% non-fat dry milk in PBS-TWEEN20® (Sigma, St. Louis, MO) (0.05%) (blocking solution) for 30 minutes at room temperature. The cells were incubated with anti-PAR antibody 10H (1:50) in Blocking solution at 37°C for 60 minutes followed by washing with PBS- TWEEN20® 5 times, and incubation with goat anti-mouse fluorescein 5(6)-isothiocyanate-coupled antibody (1:50) and 1 µg/ml 4',6-

diamidino-2-phenylindole (DAPI) in blocking solution at 37°C for 60 minutes. After washing with PBS- TWEEN20® 5 times, the analysis was performed using an FMAX FLUORESCENCE MICROPLATE READER® (Molecular Devices, Sunnyvale, CA), set at the excitation wavelength of 490 nm and emission wavelength of 528 nm fluorescein 5(6)-isothiocyanate (FITC) or the excitation wavelength of 355 nm and emission wavelength of 460 nm (DAPI). The PARP activity (FITC signal) was normalized with cell numbers (DAPI).

The cellular assay measures the formation of poly ADP-ribose by PARP within cells and demonstrates that compounds of this invention penetrate cell membranes and inhibit PARP in intact cells. The K_i data (nM) were determined from inhibition curves at various substrate concentrations and are shown in TABLE 1.

TABLE 1

Inhibition of PARP by Representative Compounds Having Formula I

Example	PARP-1 (K_i , nM)	Cell, EC_{50} , nM
1	474	
2	91	
3	83	
4	179	
5	49	39
6	11	9.6
7	6	5.4
8	99	
9	206	
10	26	12
11	127	
12	32	13
13	44	37
14	98	
15	48	29
16	51	
17	130	
18	79	
19	47	31
20	131	
21	280	

Example	PARP-1 (K_i , nM)	Cell, EC_{50} , nM
46	130	
47	2160	
48	>9500	
49	1350	
50	1960	
51	779	
52	698	
53	917	
54	635	
55	1500	
56	909	
57	1140	
58	1440	
59	534	
60	318	
61	134	
62	38	106
63	211	
64	369	
65	427	
66	23	32

Example	PARP-1 (K _i , nM)	Cell, EC ₅₀ , nM
22	330	
23	519	
24	5180	
25	2850	
26	492	
27	1120	
28	1470	
29	1500	
30	2650	
31	1490	
32	809	
33	554	
34	114	
35	63	48
36	3490	
37	98	
38	340	
39	71	
40	1500	
41	284	
42	7790	
43	97	
44	60	143
45	146	

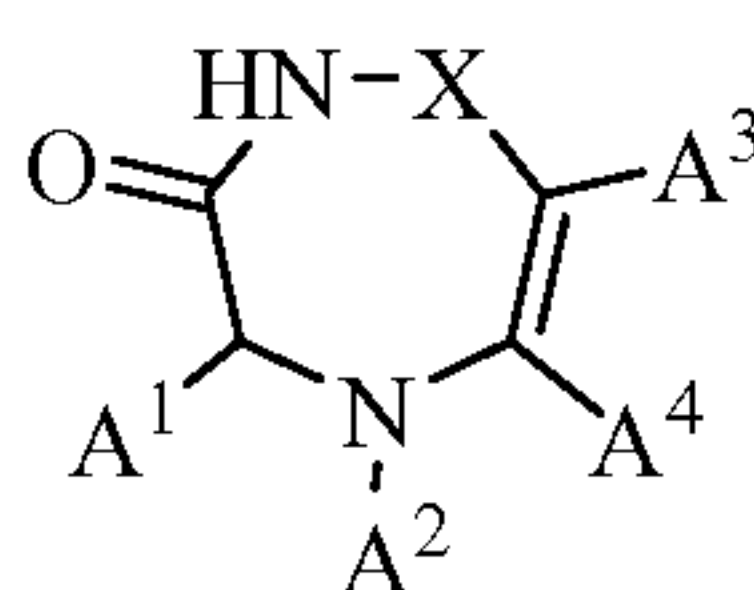
Example	PARP-1 (K _i , nM)	Cell, EC ₅₀ , nM
67	356	
68	1630	
69	129	
70	139	
71	182	
72	163	
73	874	
74	776	
75	1640	
76	149	
77	42	797
78	86	
79	615	
80	113	
81	94	
82	1540	
83	58	
84	98	
85	16	23
86	35	204
87	77	
88	8690	

As PARP inhibitors, the compounds of this invention have numerous therapeutic applications related to ischemia reperfusion injury, inflammatory diseases, degenerative diseases, protection from adverse effects of cytotoxic compounds, and potentiation of cytotoxic cancer therapy. In particular, compounds of this invention potentiate radiation and chemotherapy by increasing cell death of cancer cells, limiting tumor growth, decreasing metastasis, and prolonging the survival of tumor-bearing mammals. Compounds having fomula I can treat leukemia, colon cancer, glioblastomas, lymphomas, melanomas, carcinomas of the breast, and cervical carcinomas.

Other therapeutic applications include retroviral infection, arthritis, gout, inflammatory bowel disease, CNS inflammation, multiple sclerosis, allergic encephalitis, sepsis, septic shock, hemorrhagic shock, pulmonary fibrosis, uveitis, diabetes, Parkinsons disease, myocardial infarction, stroke, other neural trauma, organ transplantation, reperfusion of the eye, reperfusion of the kidney, reperfusion of the gut, reperfusion of skeletal muscle, liver toxicity following acetaminophen overdose, cardiac and kidney toxicities from doxorubicin and platinum based antineoplastic agents, and skin damage secondary to sulfur mustards. (G. Chen et al. Cancer Chemo. Pharmacol. 22 (1988), 303; C. Thiernemann et al., Proc. Natl. Acad. Sci. USA 94 (1997), 679-683 D. Weltin et al. Int. J. Immunopharmacol. 17 (1995), 265- 271; H. Kröger et al. Inflammation 20 (1996), 203-215; W. Ehrlich et al. Rheumatol. Int. 15 (1995), 171-172; C. Szabo et al., Proc. Natl. Acad. Sci. USA 95 (1998), 3867-3872; S. Cuzzocrea et al. Eur. J. Pharmacol. 342 (1998), 67-76; V. Burkhardt et al., Nature Medicine (1999), 5314-19).

15 Compounds of Formula I

1. In one embodiment of Formula (I)



(I),

X is a bond or CH₂;

20

A¹ and A², together with the atoms to which they are attached, are pyrrole, imidazole, piperidine, or pyrrolidine;

A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I;

30

R¹ is R², R³, R⁴ or R⁵;

R^2 is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^3 is heteroarene which is unfused or fused with benzene, heteroarene,
5 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
10

R^5 is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^6 , $C(O)OH$, NH_2 , NHR^6 , $N(R^6)_2$, $C(O)R^6$, $C(O)NH_2$, $C(O)NHR^6$, $C(O)N(R^6)_2$, $NHC(O)R^6$, $NR^6C(O)R^6$, $NR^6S(O)_2R^6$, F, Cl, Br or I;

15 R^6 is R^7 , R^8 , R^9 or R^{10} ;

R^7 is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20 R^8 is heteroarene which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene,
25 heterocycloalkane or heterocycloalkene;

R^{10} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, NH_2 , NHR^{11} , $N(R^{11})_2$, $C(O)R^{11}$, $C(O)OR^{11}$, $C(O)NH_2$, $C(O)NHR^{11}$, $C(O)N(R^{11})_2$, $NHC(O)R^{11}$, $NR^{11}C(O)R^{11}$, F, Cl, Br or
30 I;

R^{11} is R^{12} , R^{13} , R^{14} or R^{14A} ;

R^{12} is phenyl which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{13} is heteroarene which is unfused or fused with benzene, heteroarene,
5 cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene, cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;
10

R^{14A} is alkyl, alkenyl, or alkynyl;

wherein the moieties represented by A^1 and A^2 and A^3 and A^4 and the moieties represented by R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{12} , R^{13} and R^{14} are independently unsubstituted or
15 further unsubstituted or independently substituted or further substituted with R^{15} , OR^{15} , SR^{15} , $S(O)R^{15}$, SO_2R^{15} , NH_2 , NHR^{15} , $N(R^{15})_2$, $C(O)R^{15}$, $C(O)NH_2$, $C(O)NHR^{15}$, $C(O)N(R^{15})_2$, $NHC(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NHSO_2R^{15}$, $NR^{15}SO_2R^{15}$, $NHC(O)OR^{15}$, $NR^{15}C(O)OR^{15}$, SO_2NH_2 , SO_2NHR^{15} , $SO_2N(R^{15})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{15}$, $NHC(O)N(R^{15})_2$, $NR^{15}C(O)N(R^{15})_2$, OH , (O) , $C(O)OH$, CN , CF_3 , OCF_3 , CF_2CF_3 , F , Cl , Br
20 or I ;

wherein R^{15} is R^{16} , R^{17} , R^{18} or R^{19} ;

R^{16} is phenyl which is unfused or fused with benzene;
25

R^{17} is heteroaryl which is unfused or fused with benzene;

R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene;
30

R^{19} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{20} , $C(O)OH$, NH_2 , NHR^{20} or $N(R^{20})_2$, $C(O)R^{20}$, $C(O)NH_2$, $C(O)NHR^{20}$, $C(O)N(R^{20})_2$, $NHC(O)R^{20}$, $NR^{20}C(O)R^{20}$, F , Cl , Br or I ;

R^{20} is R^{21} or R^{21A} ;

R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

5

R^{21A} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{22} , $C(O)OH$, NH_2 , NHR^{22} or $N(R^{22})_2$, $C(O)R^{22}$, $C(O)NH_2$, $C(O)NHR^{22}$, $C(O)N(R^{22})_2$, $NHC(O)R^{22}$, $NR^{22}C(O)R^{22}$, F, Cl, Br or I;

10 R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

wherein the moieties represented by R^{16} , R^{17} , R^{18} , R^{21} , and R^{22} are independently unsubstituted or further unsubstituted or independently substituted or further substituted
 15 with R^{23} , OR^{23} , SR^{23} , $S(O)R^{23}$, SO_2R^{23} , NH_2 , NHR^{23} , $N(R^{23})_2$, $C(O)R^{23}$, $C(O)NH_2$, $C(O)NHR^{23}$, $C(O)N(R^{23})_2$, $NHC(O)R^{23}$, $NR^{23}C(O)R^{23}$, $NHSO_2R^{23}$, $NR^{23}SO_2R^{23}$, $NHC(O)OR^{23}$, $NR^{23}C(O)OR^{23}$, SO_2NH_2 , SO_2NHR^{23} , $SO_2N(R^{23})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{23}$, $NHC(O)N(R^{23})_2$, $NR^{23}C(O)N(R^{23})_2$, OH, (O), $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I;

20

wherein R^{23} is R^{24} , R^{25} , R^{26} or R^{27} ;

R^{24} is phenyl which is unfused or fused with benzene;

25 R^{25} is heteroaryl which is unfused or fused with benzene;

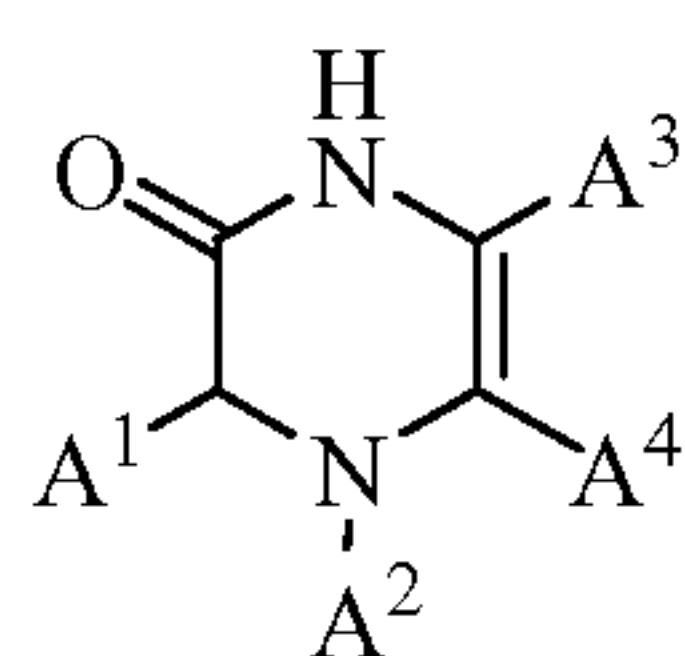
R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene;

30 R^{27} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{28} , $C(O)OH$, NH_2 , NHR^{28} or $N(R^{28})_2$, $C(O)R^{28}$, $C(O)NH_2$, $C(O)NHR^{28}$, $C(O)N(R^{28})_2$, $NHC(O)R^{28}$, $NR^{28}C(O)R^{28}$, F, Cl, Br or I;

R^{28} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or R^{29} ;

R^{29} is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected R^{30} , $C(O)OH$, NH_2 , NHR^{30} or $N(R^{30})_2$, $C(O)R^{30}$, $C(O)NH_2$, $C(O)NHR^{30}$, $C(O)N(R^{30})_2$, $NHC(O)R^{30}$, $NR^{30}C(O)R^{30}$, F, Cl, Br or I; and

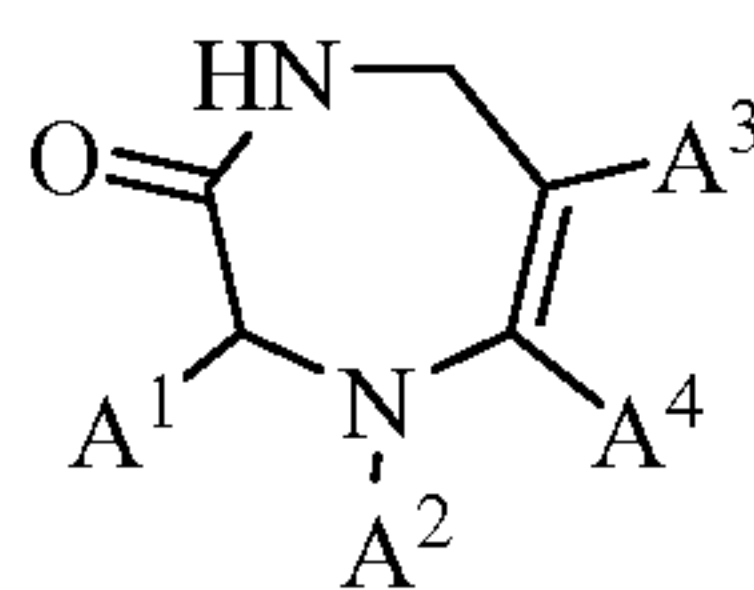
R^{30} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl.



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2. In another embodiment of Formula (I), X is a bond as in Formula (IA), and wherein A^1 , A^2 , A^3 , A^4 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



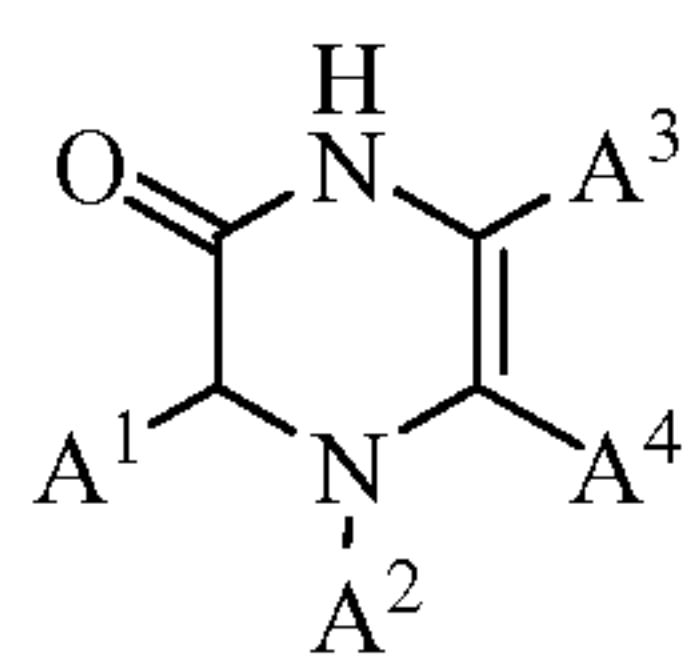
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3. In another embodiment of Formula (I), X is CH_2 as in Formula (IB), and wherein A^1 , A^2 , A^3 , A^4 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

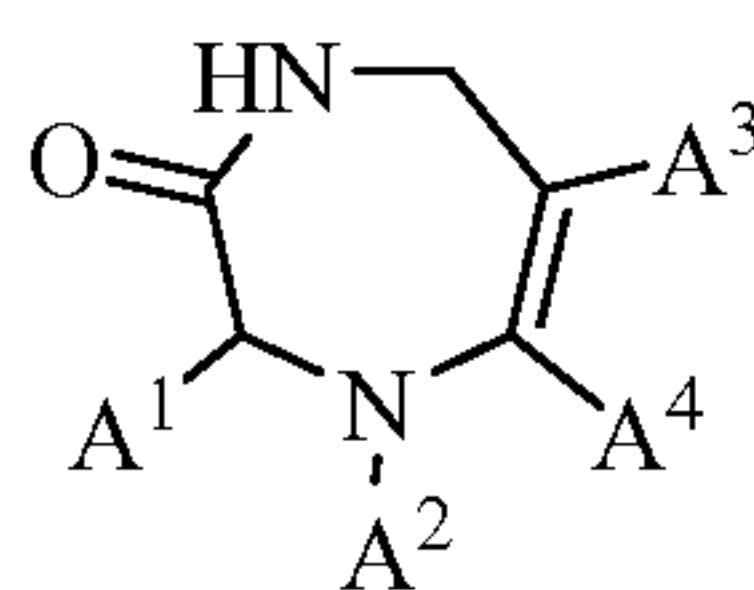
4. In another embodiment of Formula (I), A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^1 , OR^1 , SR^1 , $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, or $NR^1C(O)R^1$; and wherein X, A^1 , A^2 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

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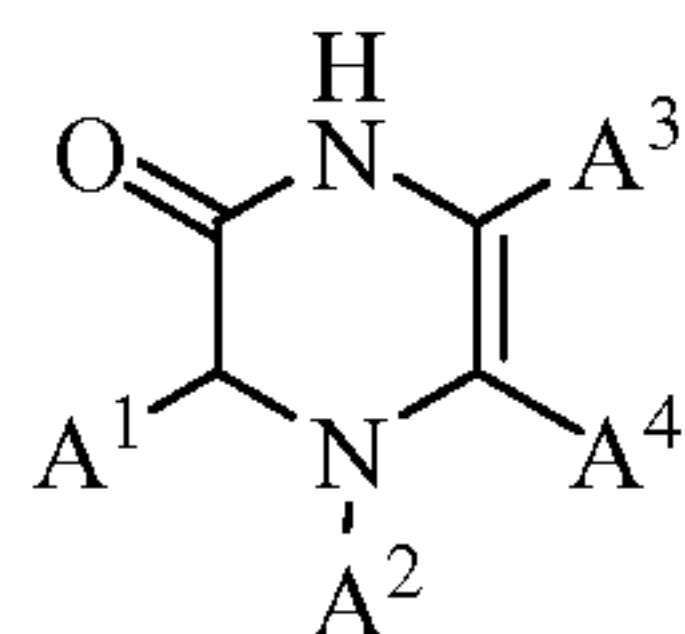
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5. In another embodiment of Formula (I), X is a bond as in Formula (1A), A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, OR¹, SR¹, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, or NR¹C(O)R¹; and wherein A¹, A², R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



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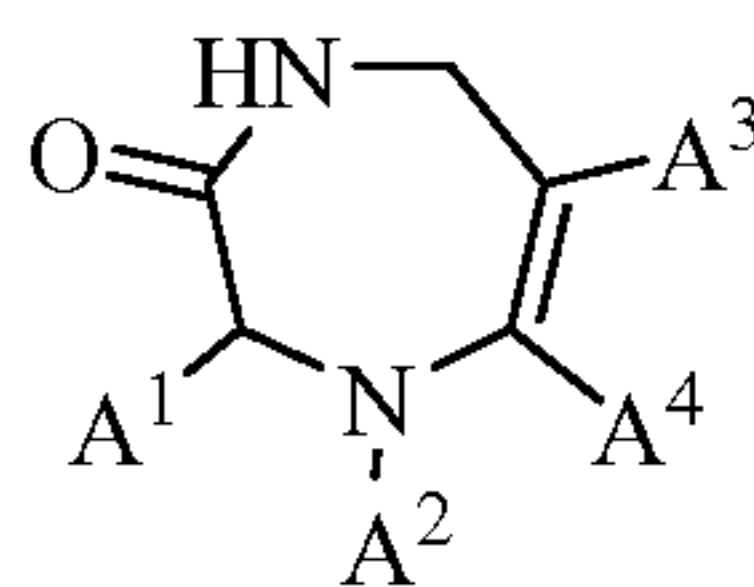
6. In another embodiment of Formula (I), X is CH₂ as in Formula (IB), A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, OR¹, SR¹, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, or NR¹C(O)R¹; and wherein A¹, A², R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).
7. In another embodiment of Formula (I), A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂; and wherein X, A¹, A², R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



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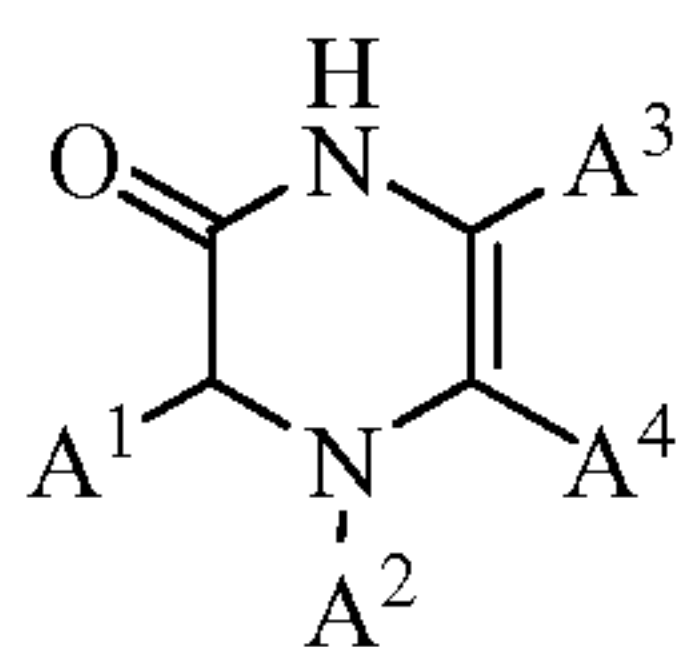
8. In another embodiment of Formula (I), X is a bond as in Formula (1A), A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂; and wherein A¹, A², R¹, R², R³, R⁴, R⁵, R⁶, R⁷,

$R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).



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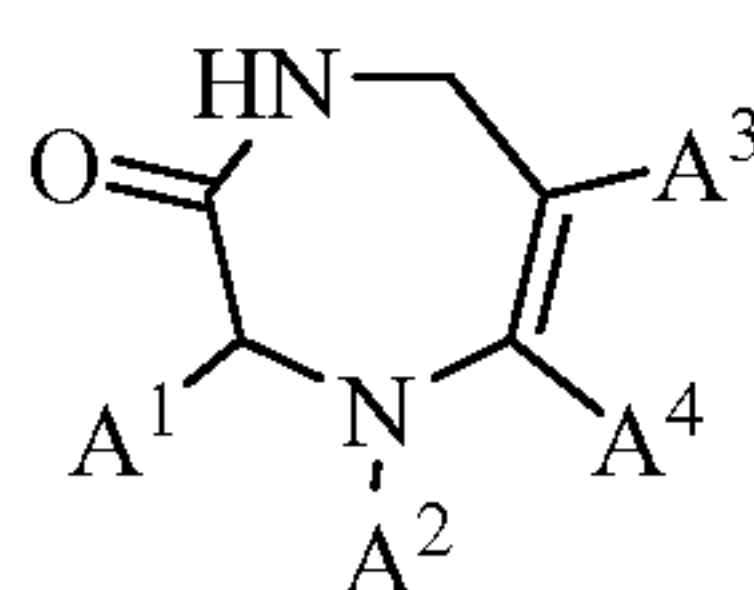
9. In another embodiment of Formula (I), X is CH_2 as in Formula (IB), A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$; and wherein $A^1, A^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).
10. In another embodiment of Formula (I), A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with $R^1, C(O)R^1, C(O)NHR^1$, or $C(O)N(R^1)_2$; R^1 is R^2, R^3, R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{12} is phenyl; R^{13} is heteroarene; R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{16} is phenyl; R^{17} is heteroaryl; R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein X, $A^1, A^2, R^5, R^6, R^{10}, R^{11}, R^{15}, R^{19}, R^{20}, R^{23}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).



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11. In another embodiment of Formula (I), X is a bond as in Formula (1A); A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with $R^1, C(O)R^1, C(O)NHR^1$, or $C(O)N(R^1)_2$; R^1 is R^2, R^3, R^4 or R^5 ; R^2 is phenyl; R^3 is

heteroarene; R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{12} is phenyl; R^{13} is heteroarene; R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{16} is phenyl; R^{17} is heteroaryl; R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein A^1 , A^2 , R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



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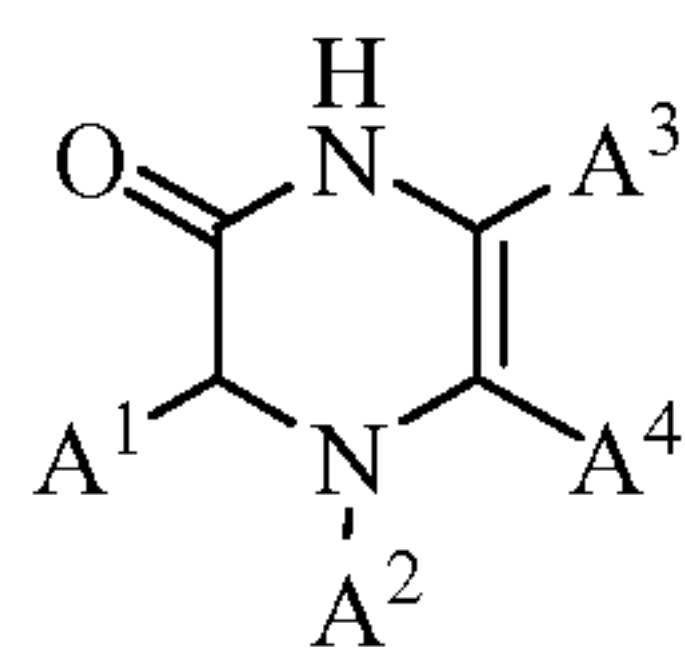
12. In another embodiment of Formula (I), X is a CH_2 ; as in Formula (1B); A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$; R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{12} is phenyl; R^{13} is heteroarene; R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{16} is phenyl; R^{17} is heteroaryl; R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein A^1 , A^2 , R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

25

13. In another embodiment of Formula (I), A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$; R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, or heterocycloalkyl; R^{12} is phenyl; R^{14} is cycloalkyl, or heterocycloalkyl; R^{18} is heterocycloalkyl; R^{28} is phenyl; and

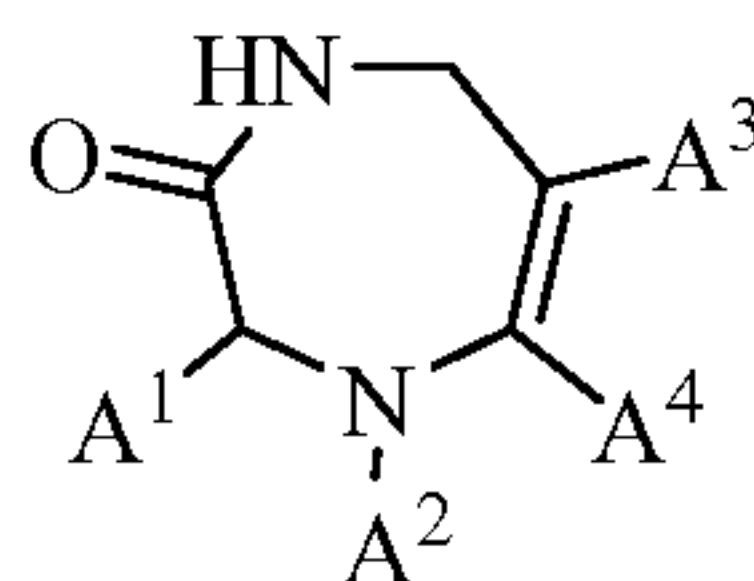
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wherein X, A¹, A², R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



IA

14. In another embodiment of Formula (I), X is a bond as in Formula (1A); A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂; R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, or heterocycloalkyl; R¹² is phenyl; R¹⁴ is cycloalkyl, or heterocycloalkyl; R¹⁸ is heterocycloalkyl; R²⁸ is phenyl; and wherein A¹, A², R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

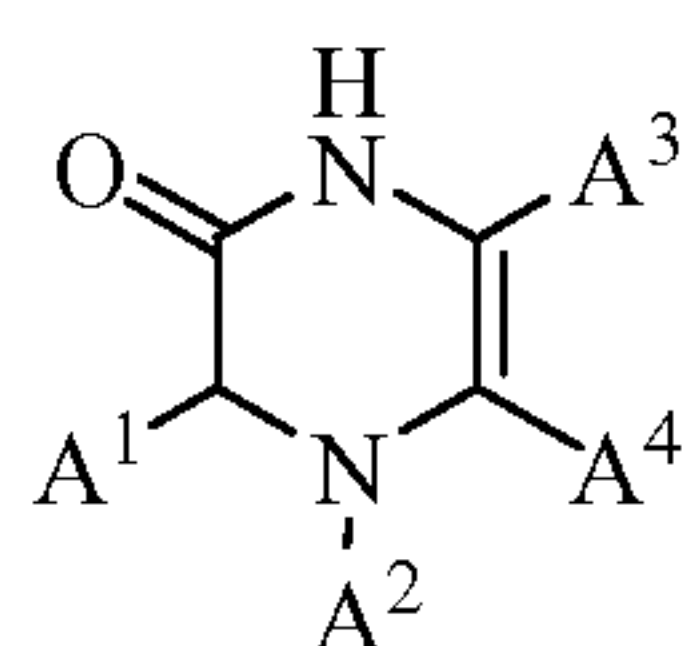


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15. In another embodiment of Formula (I), X is CH₂ as in Formula (1B); A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂; R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, or heterocycloalkyl; R¹² is phenyl; R¹⁴ is cycloalkyl, or heterocycloalkyl; R¹⁸ is heterocycloalkyl; R²⁸ is phenyl; and wherein A¹, A², R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

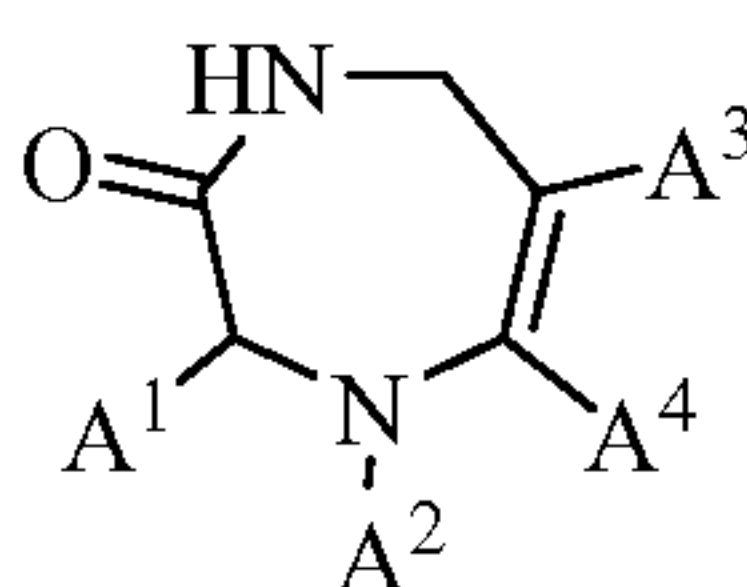
16. In another embodiment of Formula (I), X is a bond or CH₂; A¹ and A², together with the atoms to which they are attached, are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂; R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is

- heteroarene; R^9 is cycloalkyl or heterocycloalkyl; R^{10} is alkyl which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, $N(R^{11})_2$, $C(O)R^{11}$, or $C(O)OR^{11}$; R^{11} is R^{12} , R^{14} or R^{14A} ; R^{12} is phenyl; R^{14} is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R^2 , R^4 , and R^9 are independently
- 5 unsubstituted independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$, or (O) ; wherein R^{15} is R^{18} or R^{19} ; R^{18} is heterocycloalkyl; R^{19} is alkyl; wherein the moieties represented by R^{18} are independently unsubstituted or independently substituted with R^{23} ; wherein R^{23} is R^{27} ; R^{27} is alkyl each of which is substituted with R^{28} ; and R^{28} is phenyl.



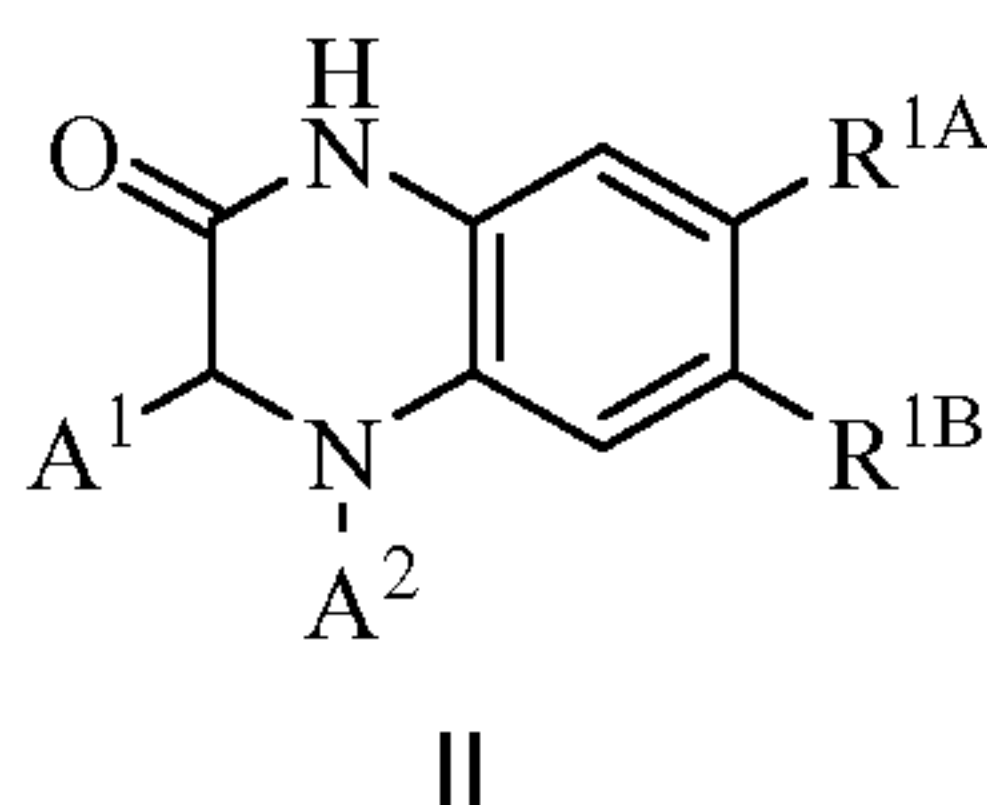
1A

- 10 17. In another embodiment of Formula (I), X is a bond as in Formula (1A); A^1 and A^2 , together with the atoms to which they are attached, are pyrrole, imidazole, piperidine, or pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$; R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^5 is alkyl which is
- 15 unsubstituted or substituted with one or two of independently selected R^6 , NHR^6 , $N(R^6)_2$, $C(O)R^6$, $NR^6C(O)R^6$, or $NR^6S(O)_2R^6$; R^6 is R^7 , R^8 , R^9 or R^{10} ; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl or heterocycloalkyl; R^{10} is alkyl which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, $N(R^{11})_2$, $C(O)R^{11}$, or $C(O)OR^{11}$; R^{11} is R^{12} , R^{14} or R^{14A} ; R^{12} is phenyl; R^{14} is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R^2 , R^4 , and R^9 are independently
- 20 unsubstituted independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$, or (O) ; wherein R^{15} is R^{18} or R^{19} ; R^{18} is heterocycloalkyl; R^{19} is alkyl; wherein the moieties represented by R^{18} are independently unsubstituted or independently substituted with R^{23} ; wherein R^{23} is R^{27} ; R^{27} is alkyl each of which is substituted with R^{28} ; and R^{28} is phenyl.

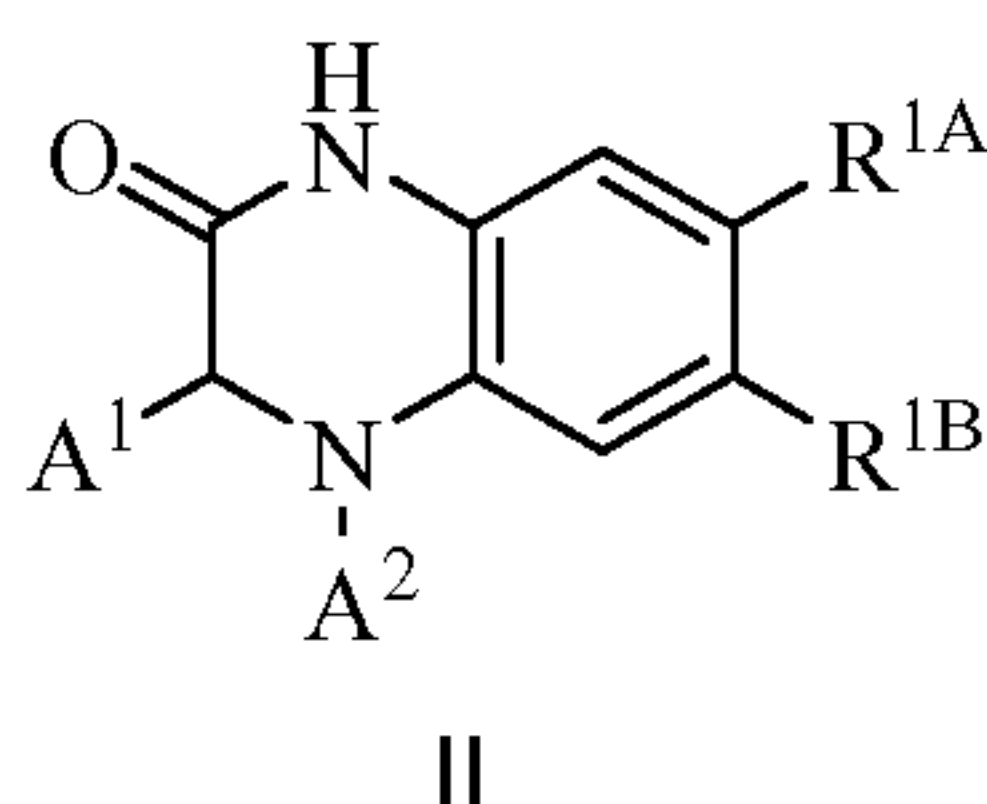


1B

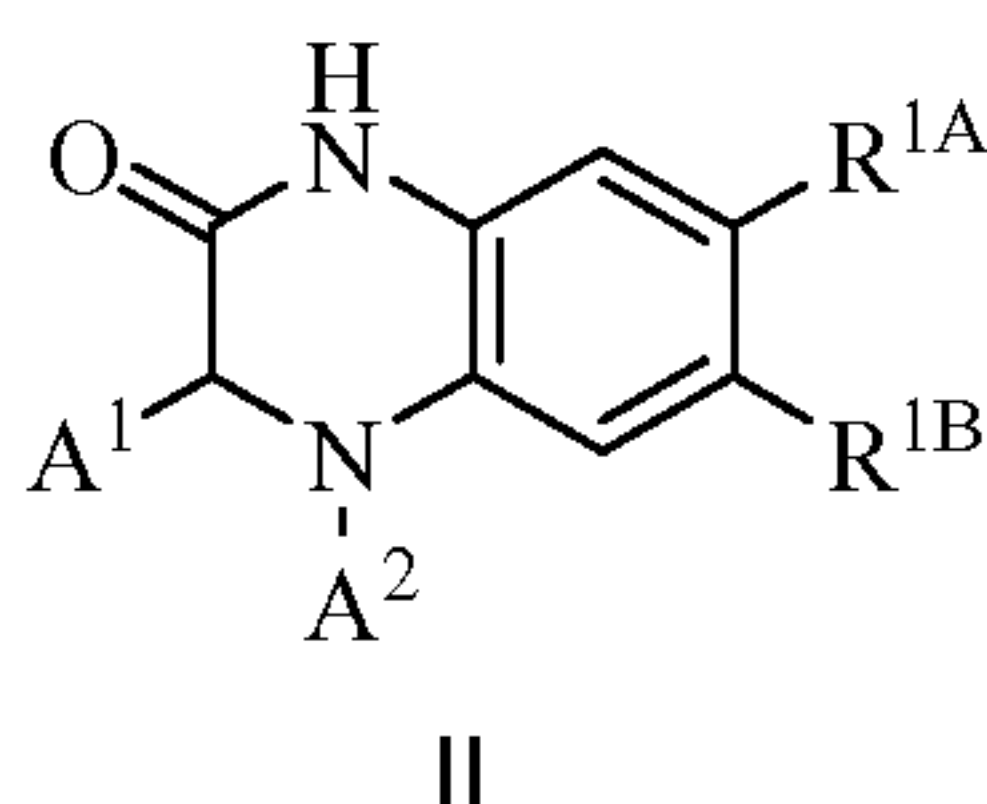
18. In another embodiment of Formula (I), X is CH₂ as in Formula (1B); A¹ and A², together with the atoms to which they are attached, are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂; R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl or heterocycloalkyl; R¹⁰ is alkyl which is unsubstituted or substituted with one or two of independently selected R¹¹, C(O)OH, N(R¹¹)₂, C(O)R¹¹, or C(O)OR¹¹; R¹¹ is R¹², R¹⁴ or R^{14A}; R¹² is phenyl; R¹⁴ is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R², R⁴, and R⁹ are independently unsubstituted independently substituted with R¹⁵, SO₂R¹⁵, NH₂, N(R¹⁵)₂, or (O); wherein R¹⁵ is R¹⁸ or R¹⁹; R¹⁸ is heterocycloalkyl; R¹⁹ is alkyl; wherein the moieties represented by R¹⁸ are independently unsubstituted or independently substituted with R²³; wherein R²³ is R²⁷; R²⁷ is alkyl each of which is substituted with R²⁸; and R²⁸ is phenyl.



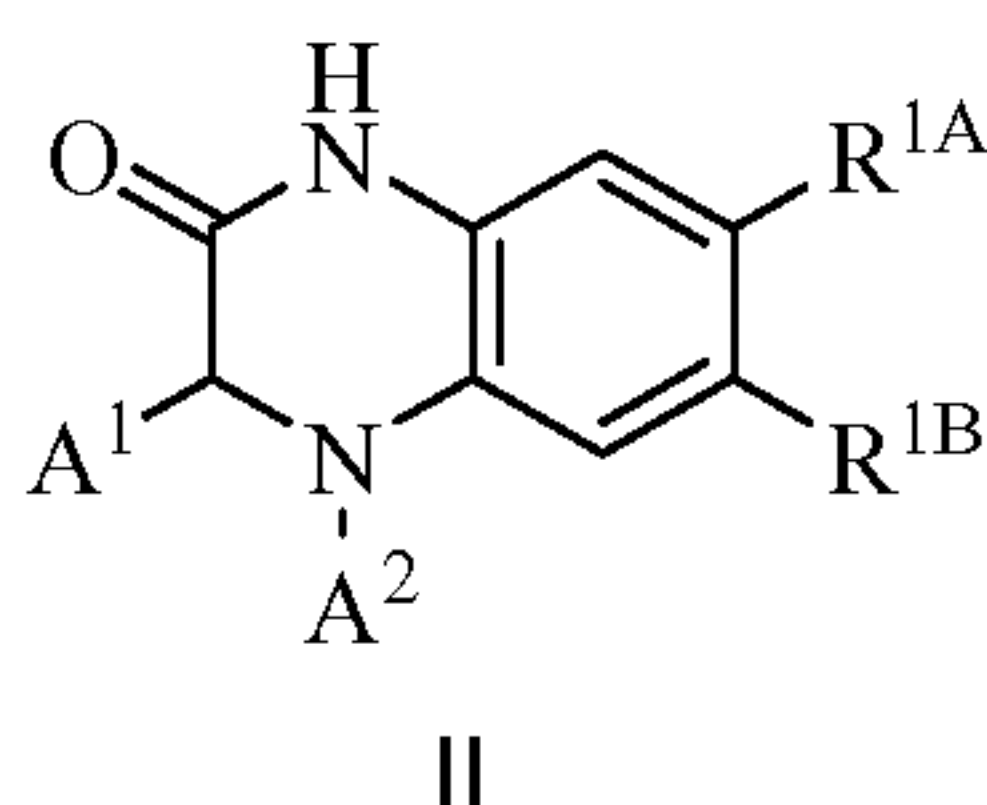
19. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}, and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I as in Formula (II); wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



20. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}, and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, C(O)R¹,
 5 C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, or NR¹C(O)R¹ as in Formula (II); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

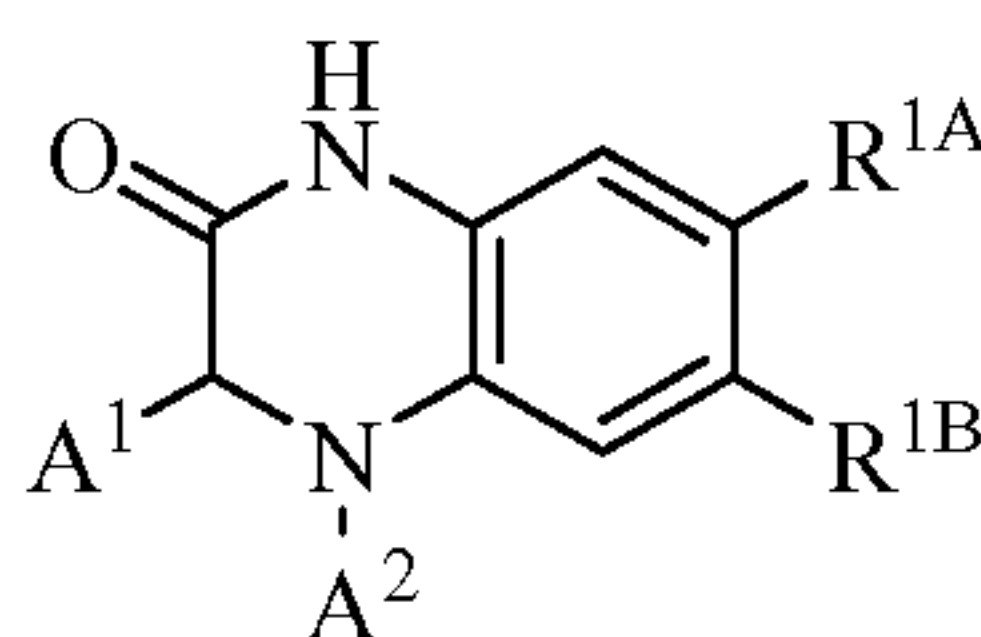


21. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the
 10 atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (II); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰
 15 are as described in Formula (I).



22. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted
 20 with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (II); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹² is phenyl; R¹³ is heteroarene; R¹⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or
 25 heterocycloalkenyl; R¹⁶ is phenyl; R¹⁷ is heteroaryl; R¹⁸ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²¹ is phenyl, heteroaryl, cycloalkyl, cycloalkenyl,

heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

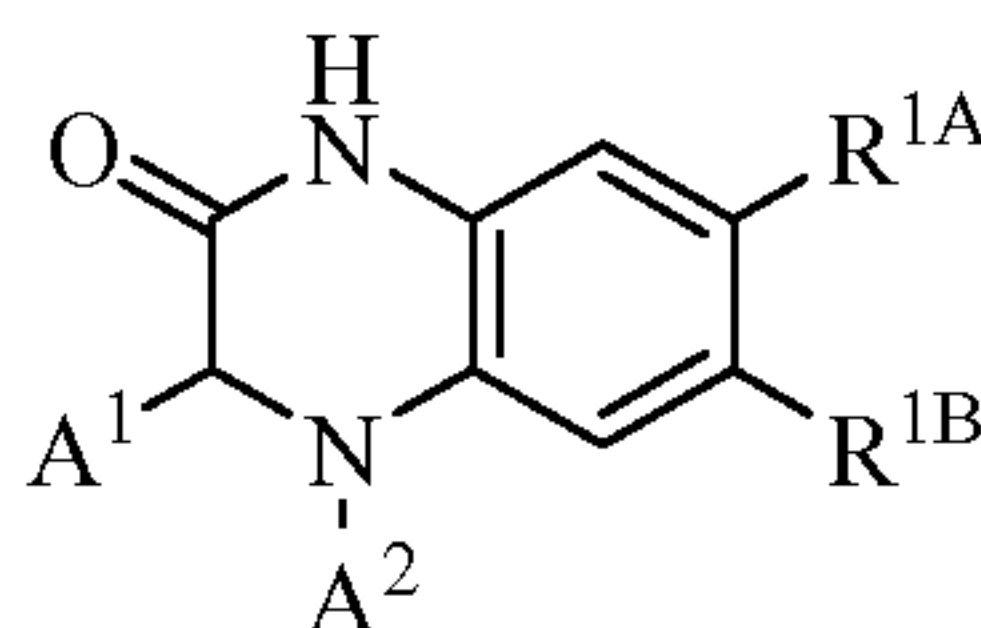


II

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23. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (II); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, or heterocycloalkyl; R^{12} is phenyl; R^{14} is cycloalkyl, or heterocycloalkyl; R^{18} is heterocycloalkyl; R^{28} is phenyl; and wherein R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

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II

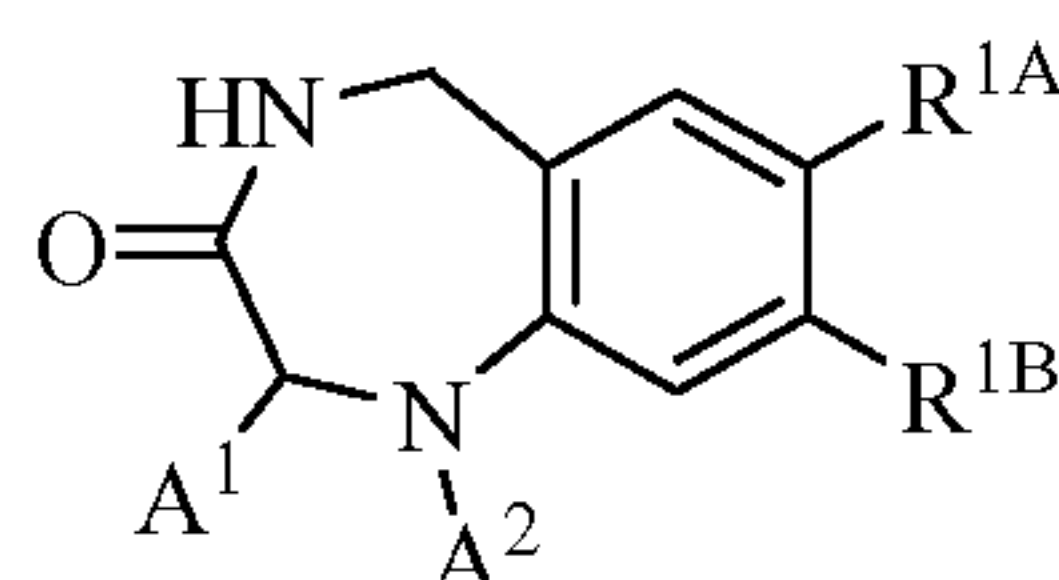
15

24. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (II); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^5 is alkyl which is unsubstituted or substituted with one or two of independently selected R^6 , NHR^6 , $N(R^6)_2$, $C(O)R^6$, $NR^6C(O)R^6$, or $NR^6S(O)_2R^6$; R^6 is R^7 , R^8 , R^9 or R^{10} ; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl or heterocycloalkyl; R^{10} is alkyl which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, $N(R^{11})_2$, $C(O)R^{11}$, or $C(O)OR^{11}$; R^{11} is R^{12} , R^{14} or R^{14A} ; R^{12} is phenyl; R^{14} is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the

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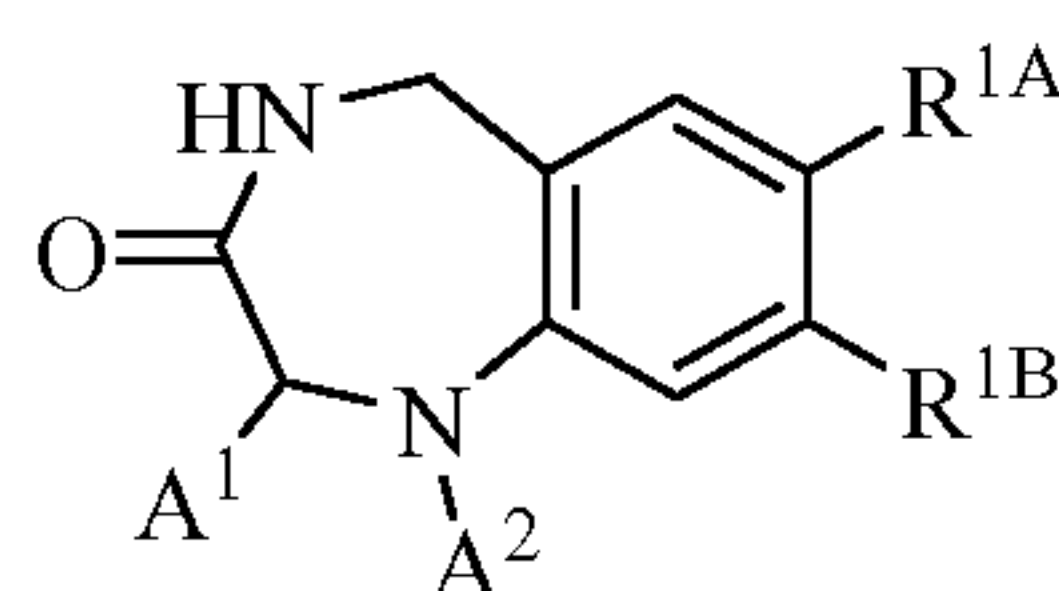
25

moieties represented by R^2 , R^4 , and R^9 are independently unsubstituted independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$, or (O); wherein R^{15} is R^{18} or R^{19} ; R^{18} is heterocycloalkyl; R^{19} is alkyl; wherein the moieties represented by R^{18} are independently unsubstituted or independently substituted with R^{23} ; wherein R^{23} is R^{27} ; R^{27} is alkyl each
 5 of which is substituted with R^{28} ; and R^{28} is phenyl.



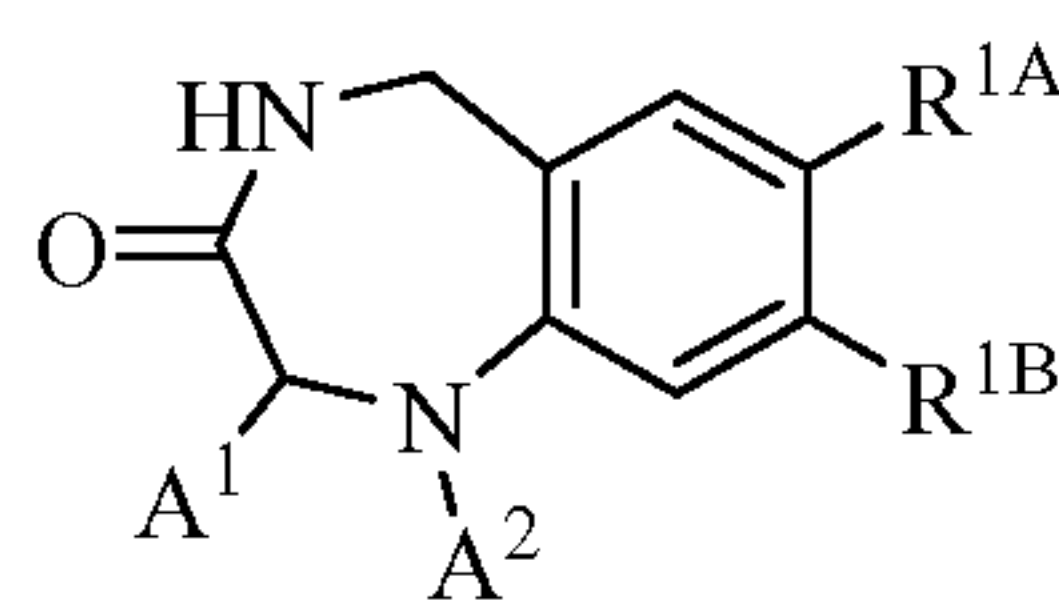
III

25. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted
 10 with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $S(O)R^1$, SO_2R^1 , NH_2 , NHR^1 , $N(R^1)_2$, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, OH, $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I as in Formula (III); wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} ,
 15 R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



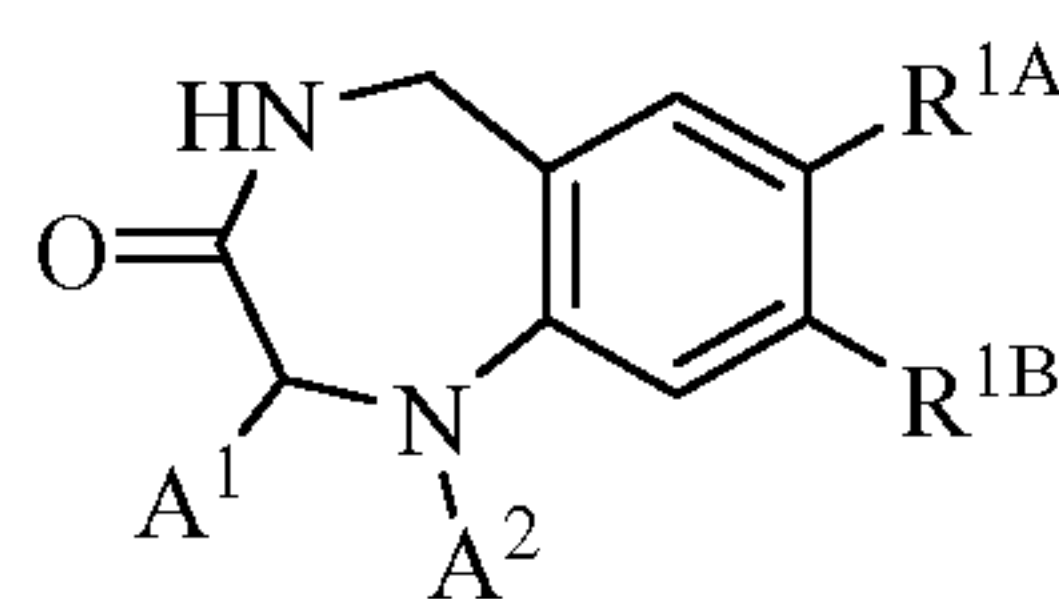
III

26. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A^3 and
 20 A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, or $NR^1C(O)R^1$ as in Formula (III); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



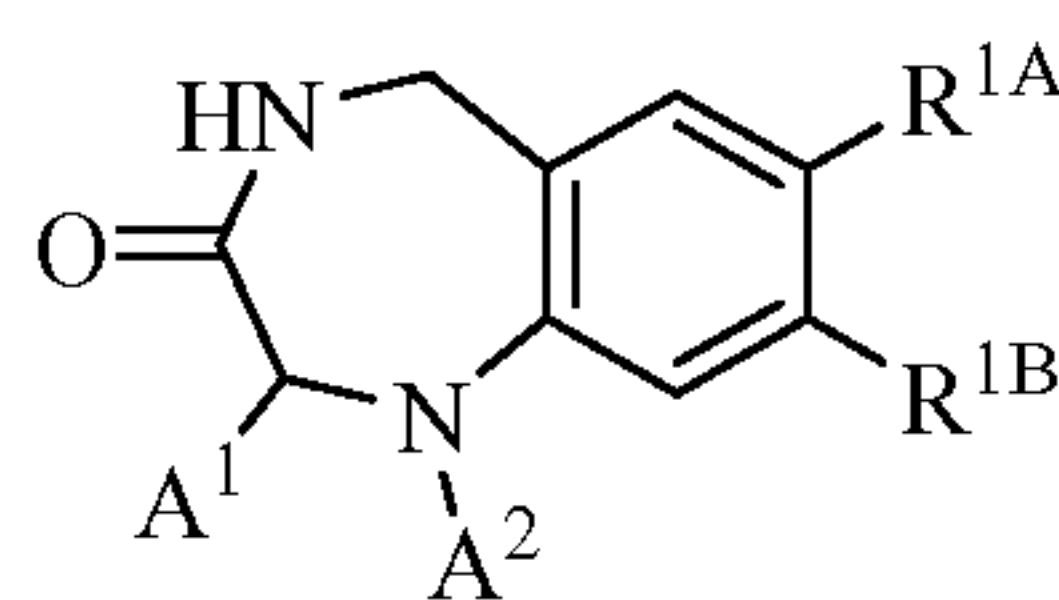
III

27. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (III); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



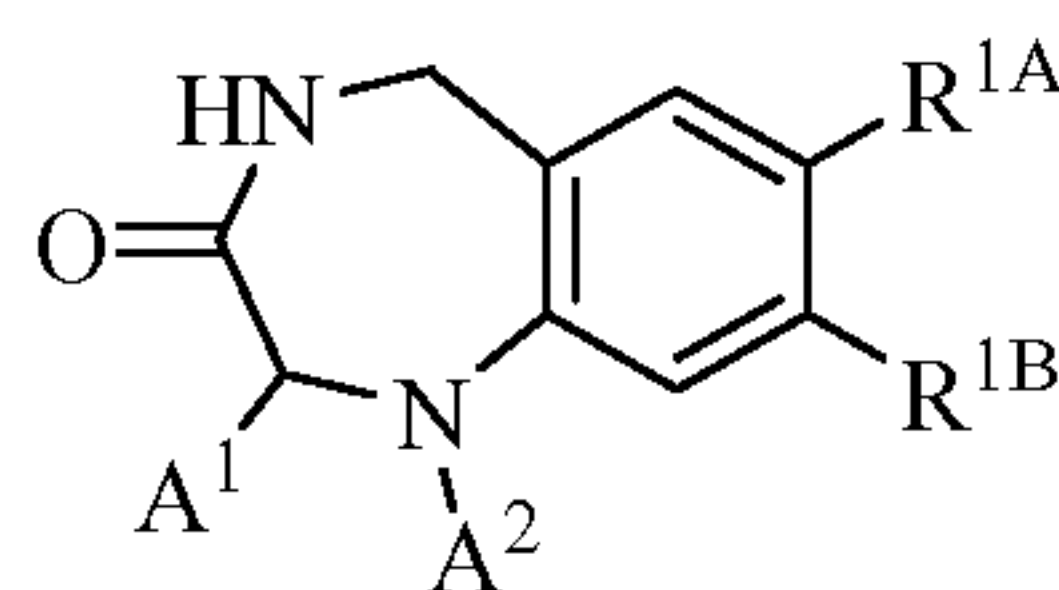
III

28. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (III); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹² is phenyl; R¹³ is heteroarene; R¹⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹⁶ is phenyl; R¹⁷ is heteroaryl; R¹⁸ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²¹ is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R²² is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²⁴ is phenyl; R²⁵ is heteroaryl; and R²⁶ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



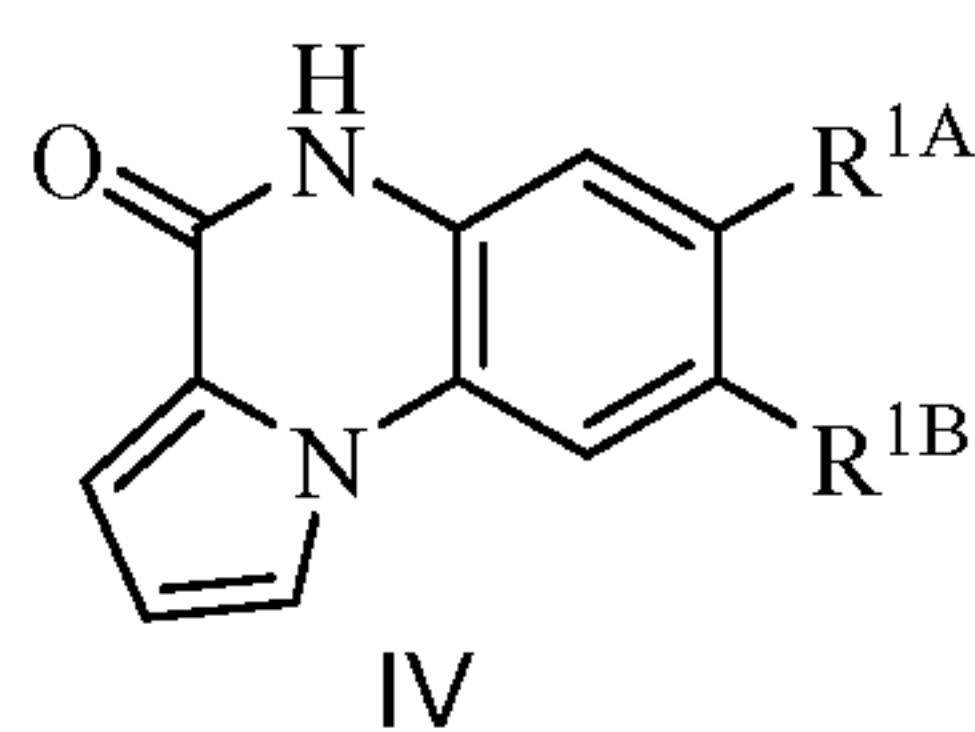
III

29. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (III); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, or heterocycloalkyl; R¹² is phenyl; R¹⁴ is cycloalkyl, or heterocycloalkyl; R¹⁸ is heterocycloalkyl; R²⁸ is phenyl; and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

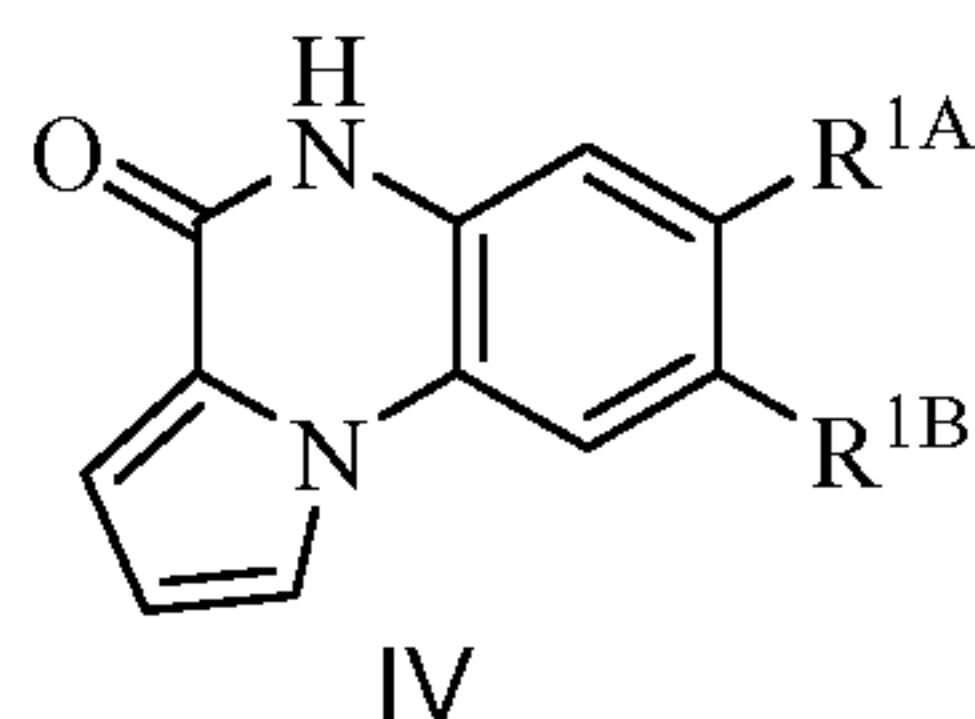


III

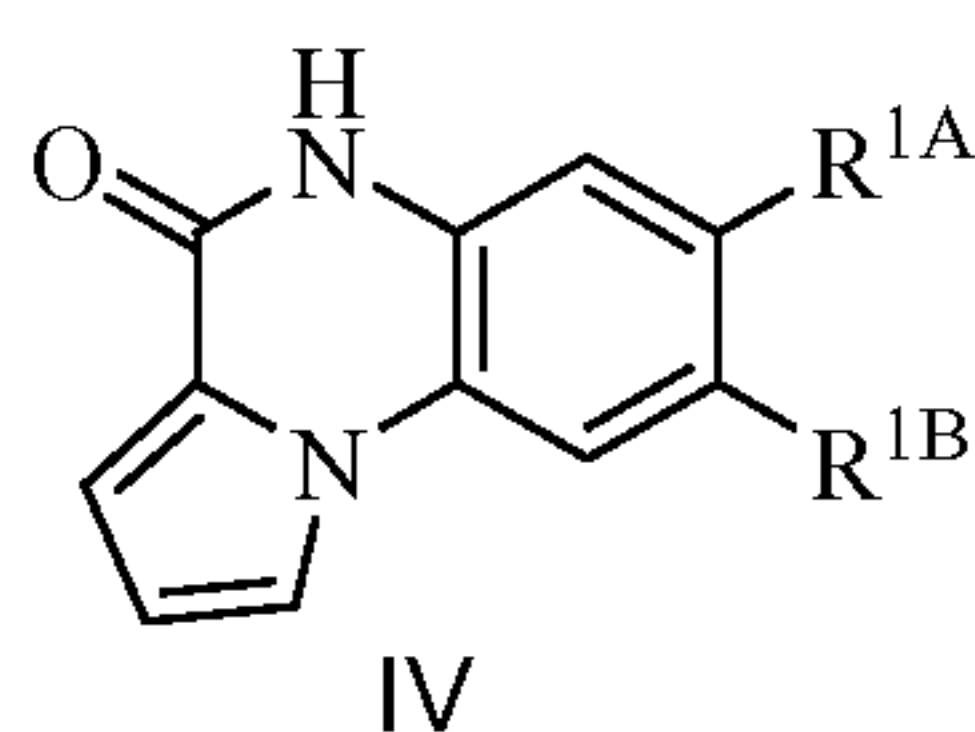
30. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are pyrrole, imidazole, piperidine, or pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (III); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl or heterocycloalkyl; R¹⁰ is alkyl which is unsubstituted or substituted with one or two of independently selected R¹¹, C(O)OH, N(R¹¹)₂, C(O)R¹¹, or C(O)OR¹¹; R¹¹ is R¹², R¹⁴ or R^{14A}; R¹² is phenyl; R¹⁴ is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R², R⁴, and R⁹ are independently unsubstituted independently substituted with R¹⁵, SO₂R¹⁵, NH₂, N(R¹⁵)₂, or (O); wherein R¹⁵ is R¹⁸ or R¹⁹; R¹⁸ is heterocycloalkyl; R¹⁹ is alkyl; wherein the moieties represented by R¹⁸ are independently unsubstituted or independently substituted with R²³; wherein R²³ is R²⁷; R²⁷ is alkyl each of which is substituted with R²⁸; and R²⁸ is phenyl.



31. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I as in Formula (IV); wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

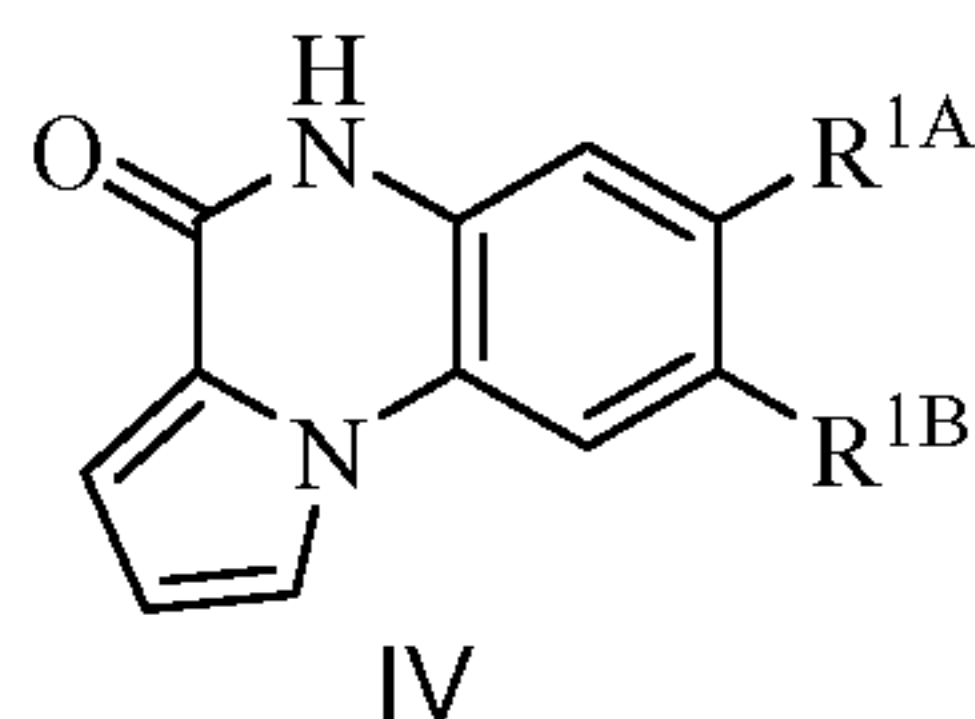


32. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, or NR¹C(O)R¹ as in Formula (IV); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

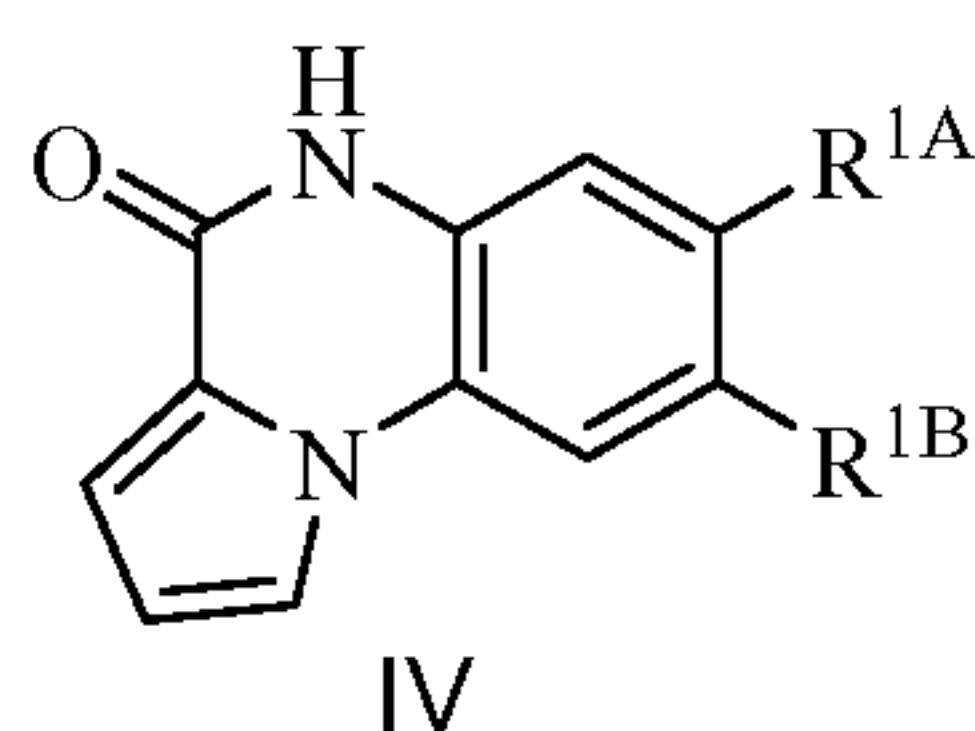


33. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (IV); and

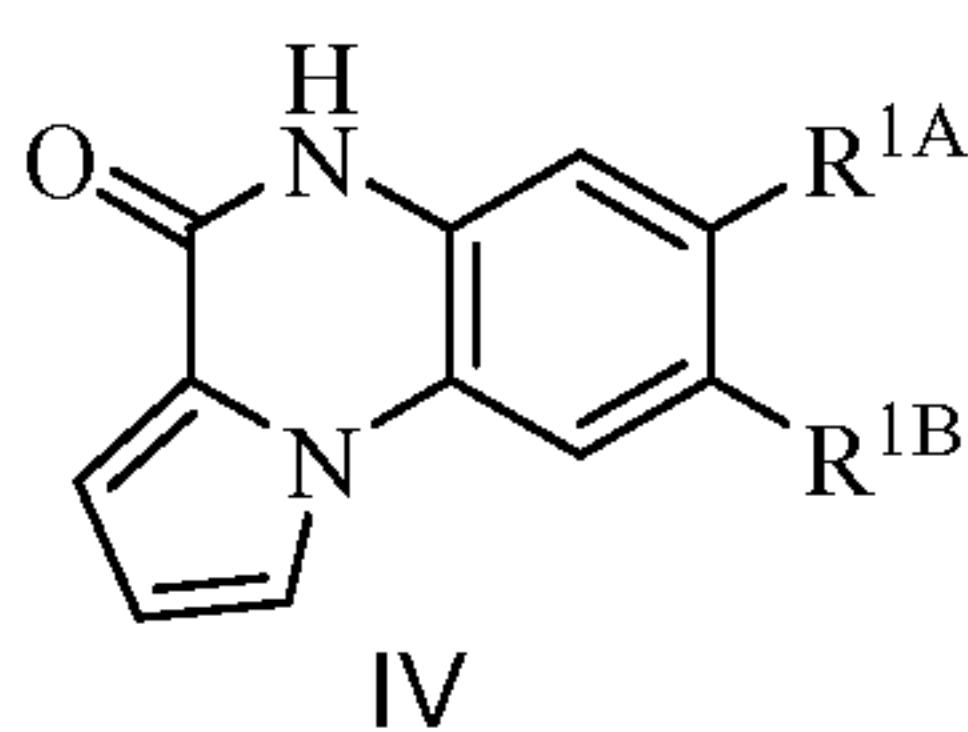
wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).



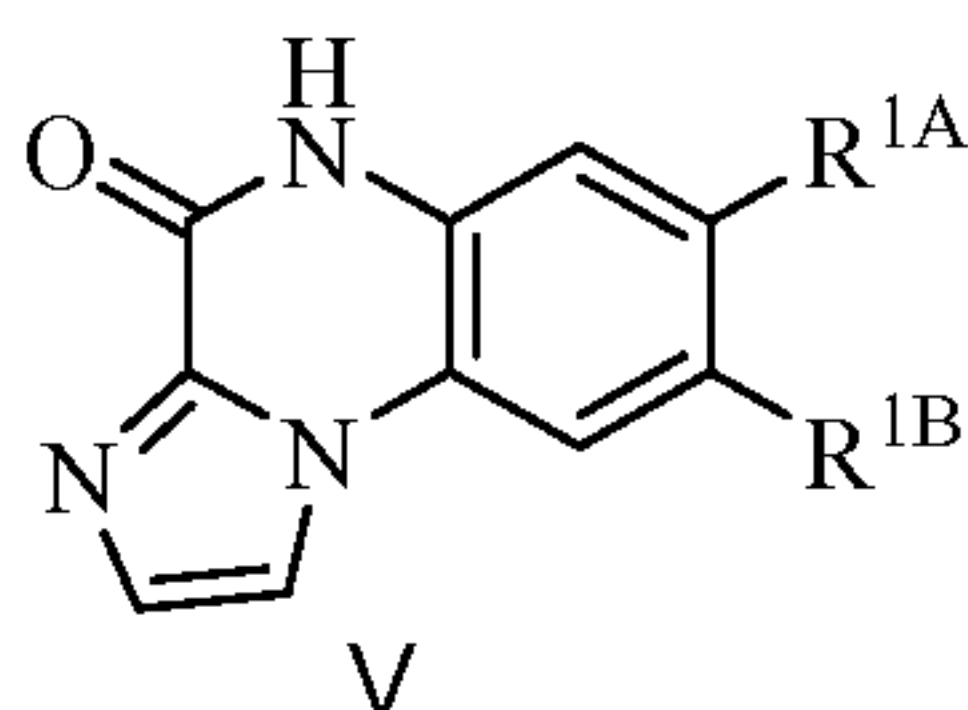
34. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the
 5 atoms to which they are attached are pyrrole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is $R^1, C(O)R^1, C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (IV); and R^1 is R^2, R^3, R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^7 is phenyl; R^8 is heteroarene; R^9 is
 10 cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{12} is phenyl; R^{13} is heteroarene; R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{16} is phenyl; R^{17} is heteroaryl; R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl,
 15 heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein $R^5, R^6, R^{10}, R^{11}, R^{15}, R^{19}, R^{20}, R^{23}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).



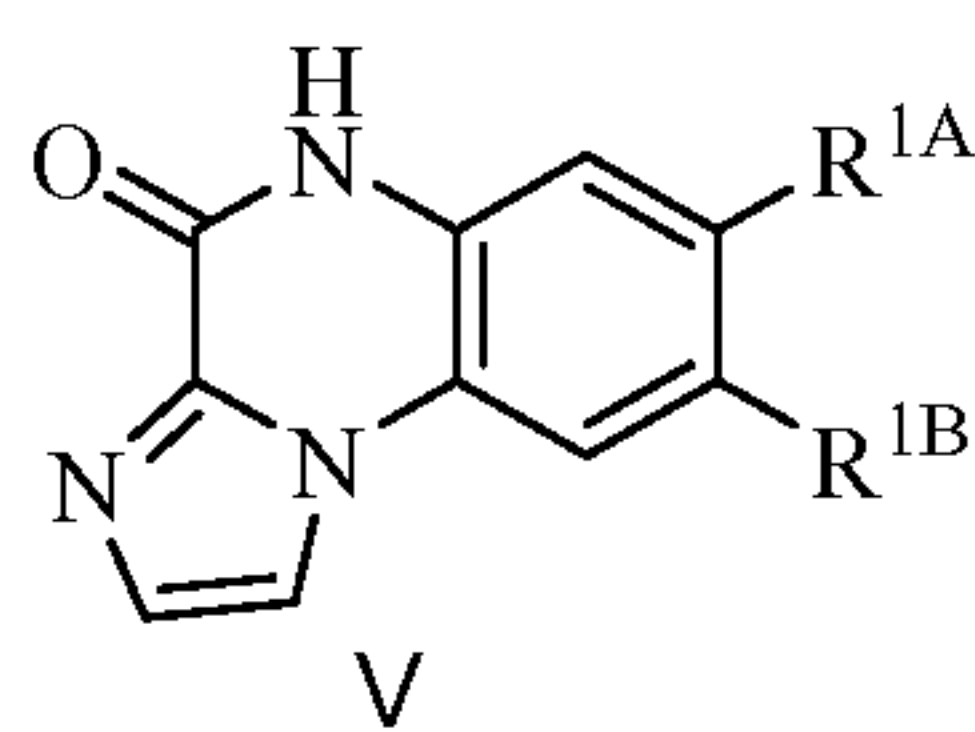
35. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the
 20 atoms to which they are attached are pyrrole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is $R^1, C(O)R^1, C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (IV); and R^1 is R^2, R^3, R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, or heterocycloalkyl; R^{12} is phenyl; R^{14} is
 25 cycloalkyl, or heterocycloalkyl; R^{18} is heterocycloalkyl; R^{28} is phenyl; and wherein $R^5, R^6, R^{10}, R^{11}, R^{15}, R^{19}, R^{20}, R^{23}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).



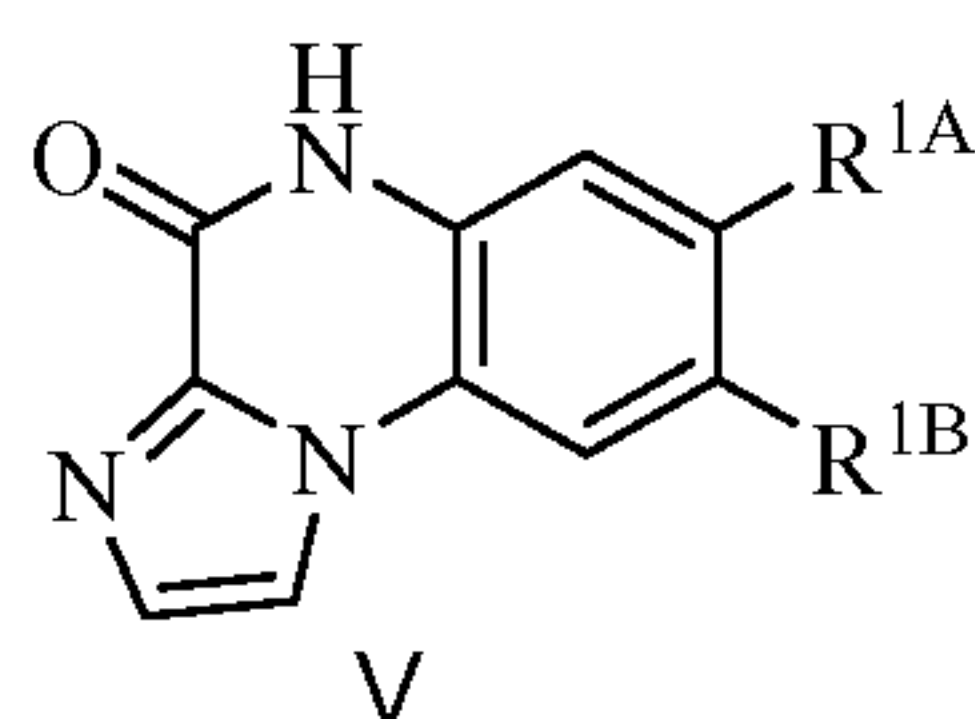
36. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (IV); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl or heterocycloalkyl; R¹⁰ is alkyl which is unsubstituted or substituted with one or two of independently selected R¹¹, C(O)OH, N(R¹¹)₂, C(O)R¹¹, or C(O)OR¹¹; R¹¹ is R¹², R¹⁴ or R^{14A}; R¹² is phenyl; R¹⁴ is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R², R⁴, and R⁹ are independently unsubstituted independently substituted with R¹⁵, SO₂R¹⁵, NH₂, N(R¹⁵)₂, or (O); wherein R¹⁵ is R¹⁸ or R¹⁹; R¹⁸ is heterocycloalkyl; R¹⁹ is alkyl; wherein the moieties represented by R¹⁸ are independently unsubstituted or independently substituted with R²³; wherein R²³ is R²⁷; R²⁷ is alkyl each of which is substituted with R²⁸; and R²⁸ is phenyl.



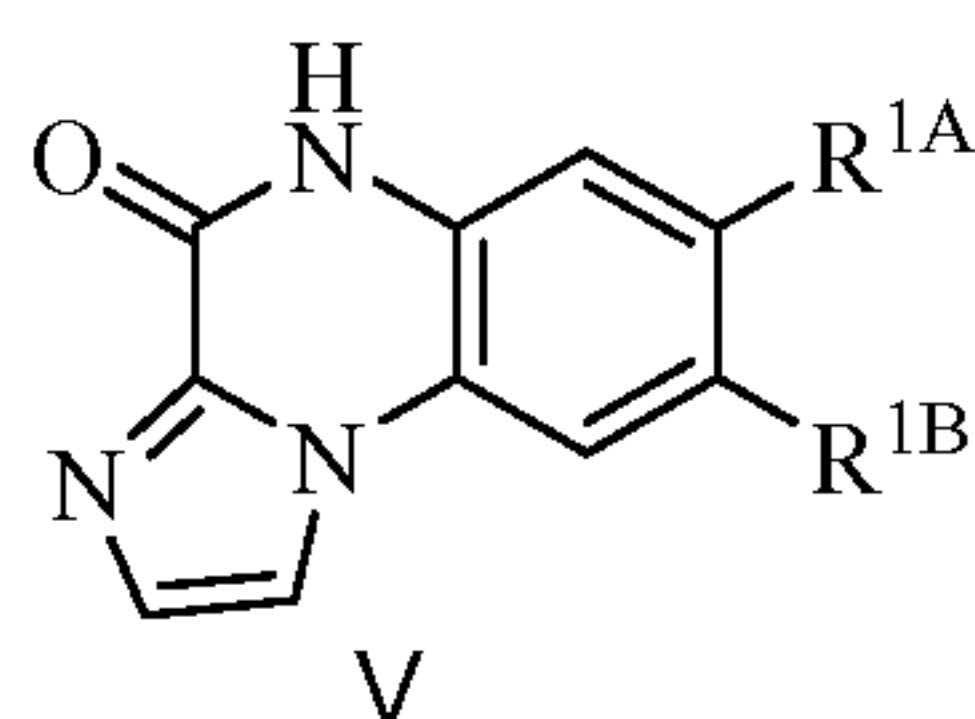
37. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I as in Formula (V); wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



38. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, or NR¹C(O)R¹ as in Formula (V); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

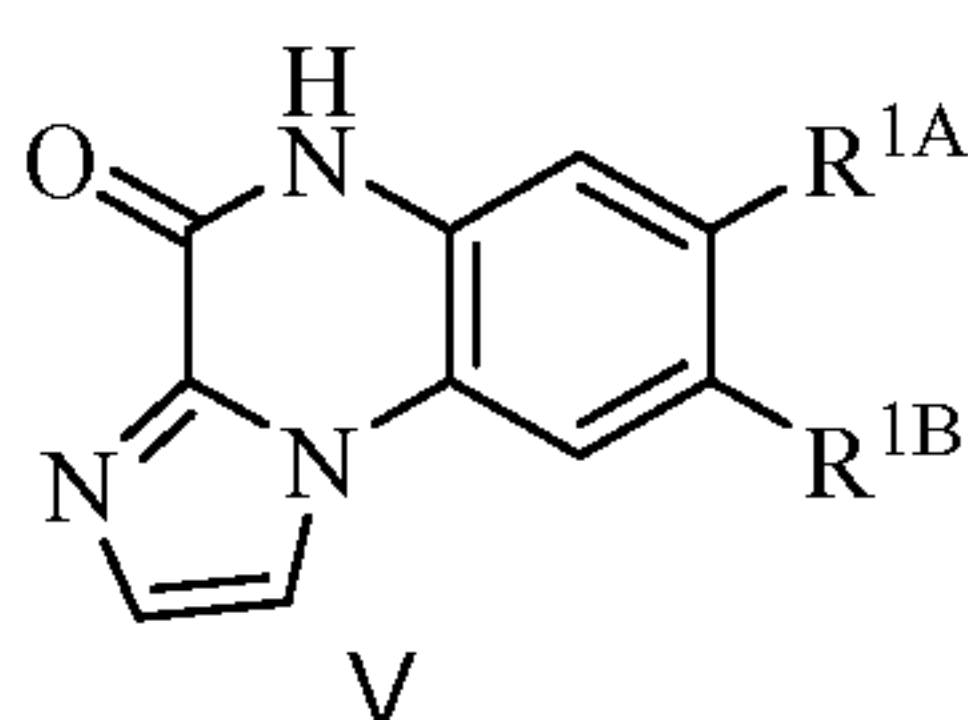


39. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (V); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

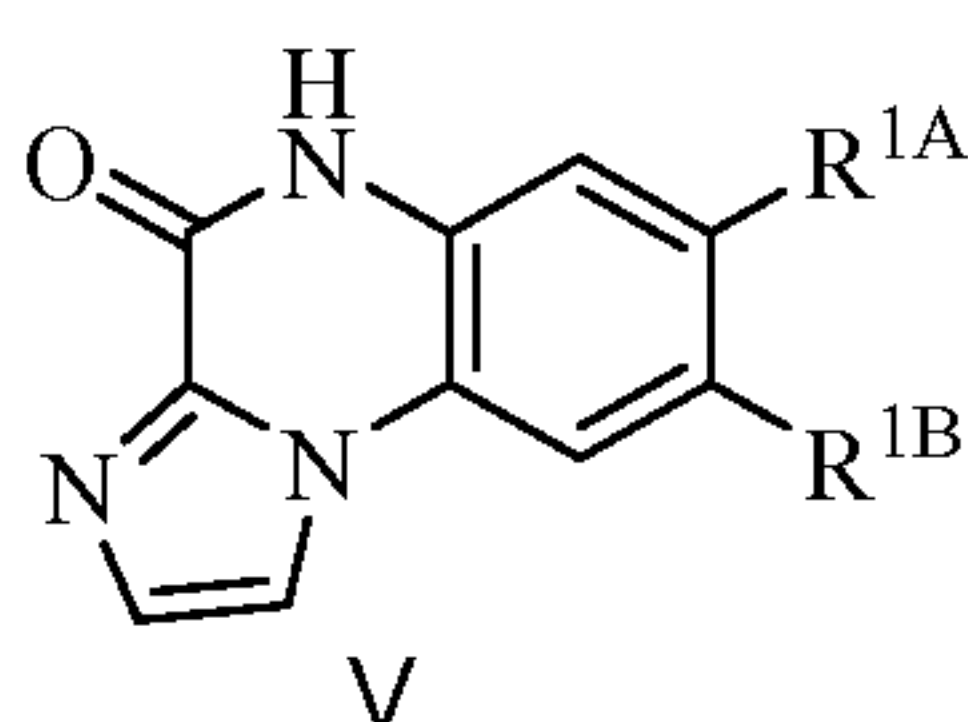


40. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (V); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹² is

- phenyl; R¹³ is heteroarene; R¹⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹⁶ is phenyl; R¹⁷ is heteroaryl; R¹⁸ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²¹ is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R²² is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²⁴ is phenyl; R²⁵ is heteroaryl; and R²⁶ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

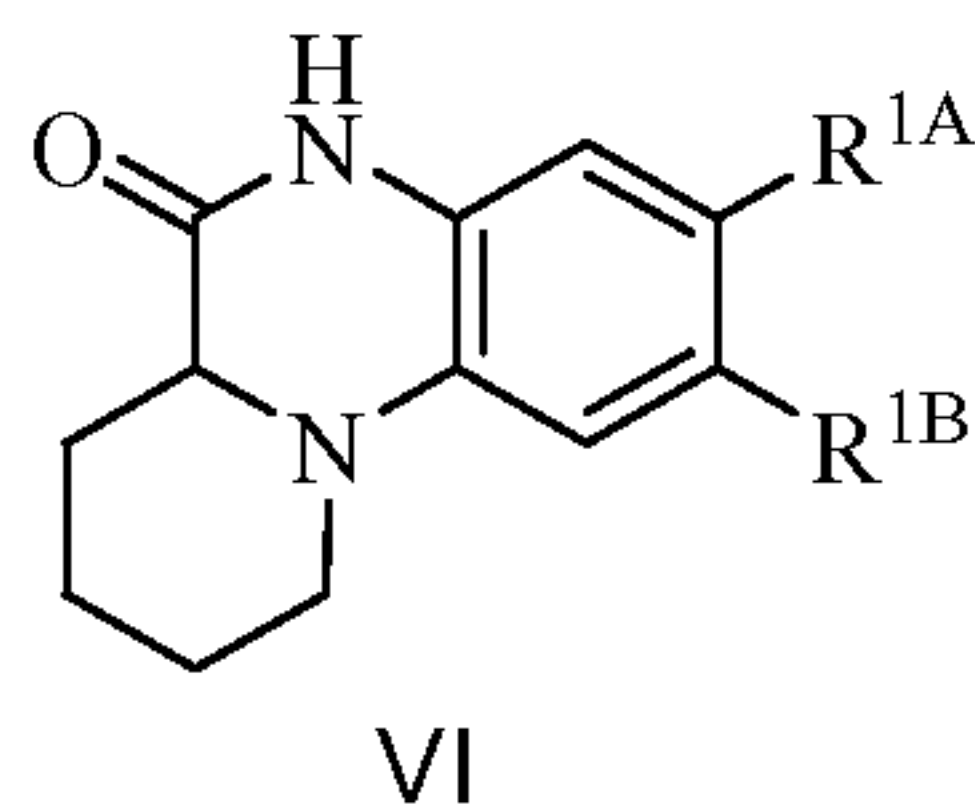


41. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (V); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, or heterocycloalkyl; R¹² is phenyl; R¹⁴ is cycloalkyl, or heterocycloalkyl; R¹⁸ is heterocycloalkyl; R²⁸ is phenyl; and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

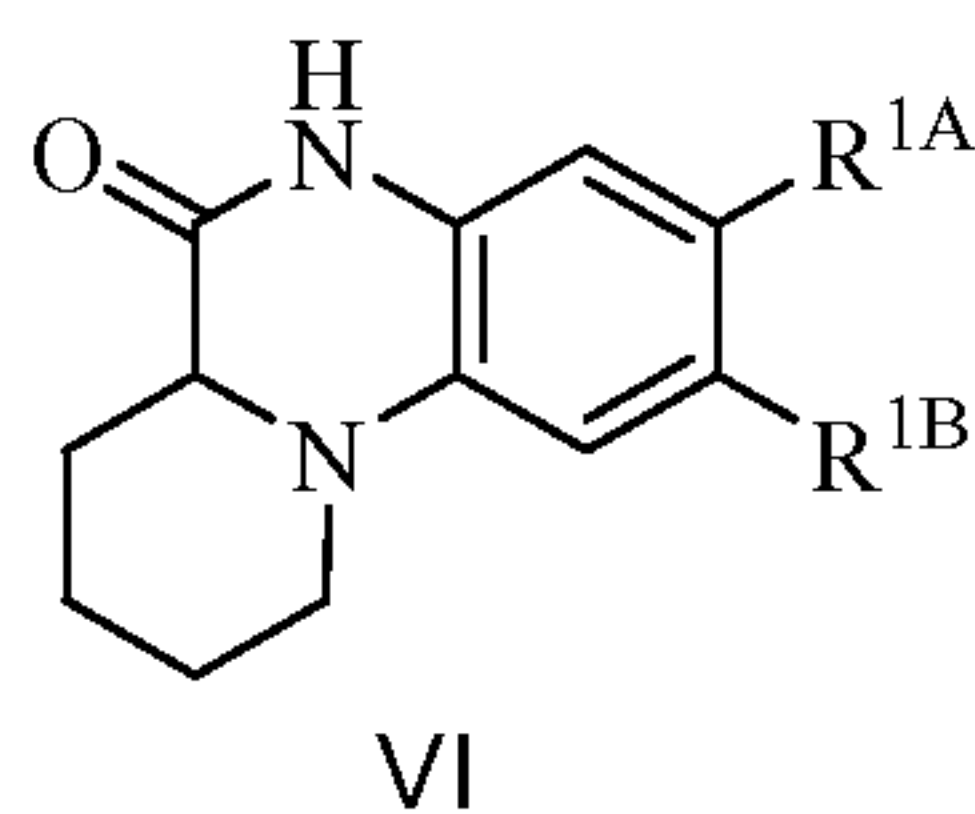


42. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (V); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl or heterocycloalkyl; R¹⁰ is alkyl which is unsubstituted or substituted with one or two of independently selected R¹¹, C(O)OH, N(R¹¹)₂, C(O)R¹¹, or C(O)OR¹¹; R¹¹ is R¹², R¹⁴ or R^{14A}; R¹² is phenyl; R¹⁴ is

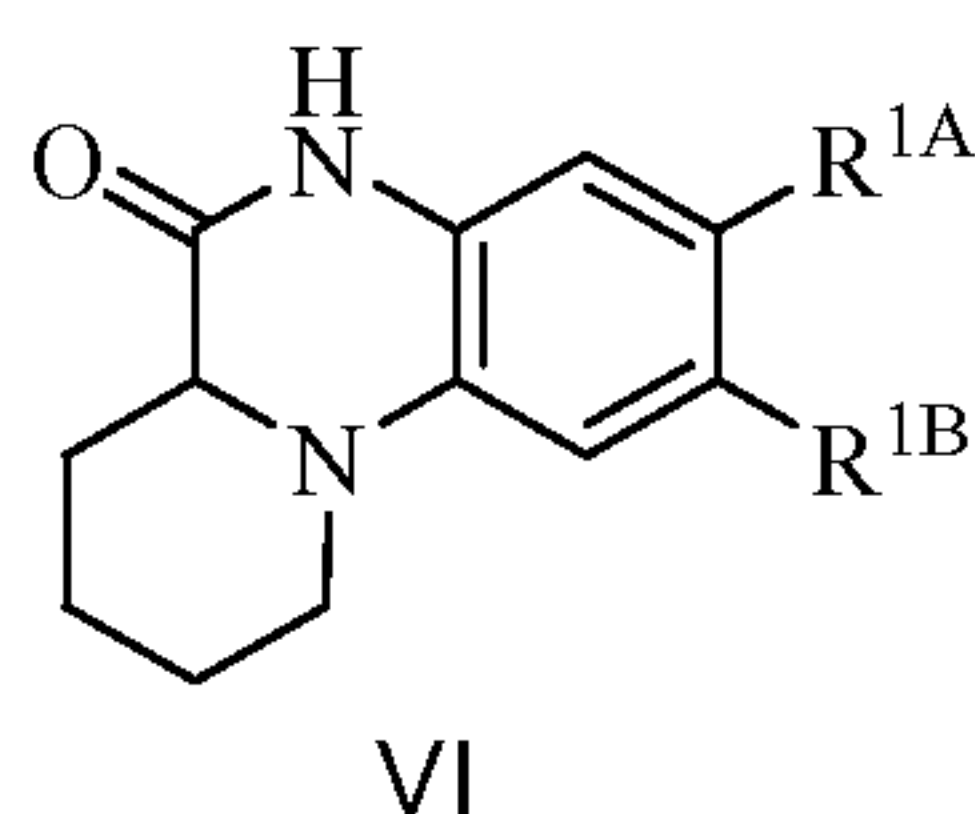
cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R^2 , R^4 , and R^9 are independently unsubstituted independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$, or (O); wherein R^{15} is R^{18} or R^{19} ; R^{18} is heterocycloalkyl; R^{19} is alkyl; wherein the moieties represented by R^{18} are independently unsubstituted or independently substituted with R^{23} ; wherein R^{23} is R^{27} ; R^{27} is alkyl each of which is substituted with R^{28} ; and R^{28} is phenyl.



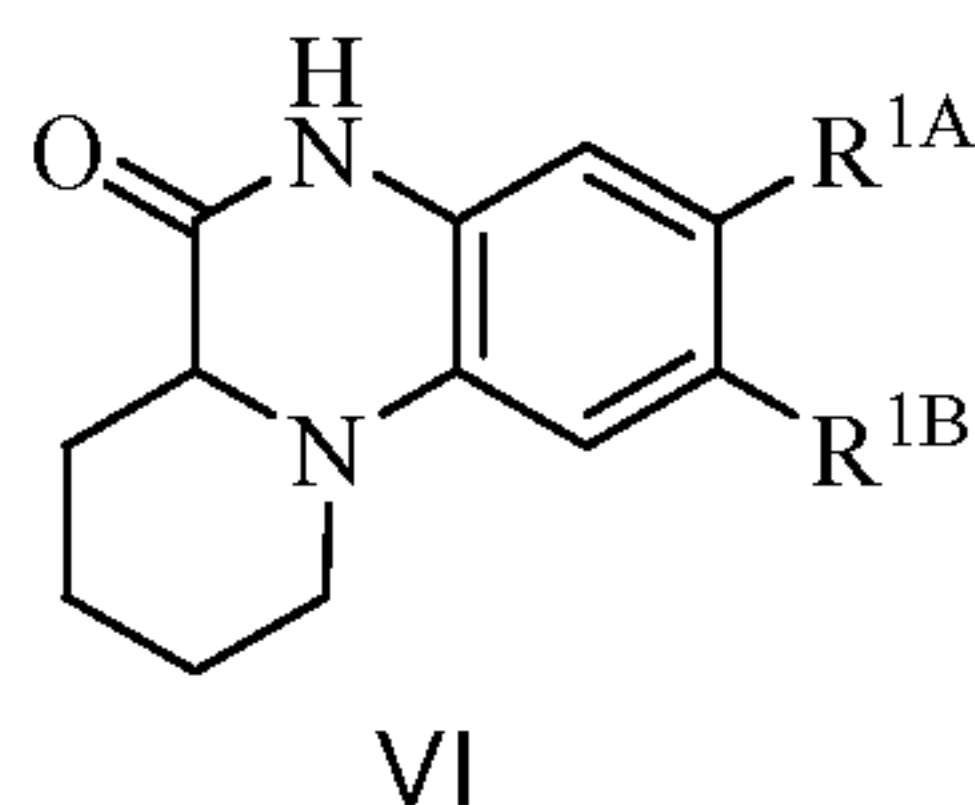
43. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the atoms to which they are attached are piperidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $S(O)R^1$, SO_2R^1 , NH_2 , NHR^1 , $N(R^1)_2$, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, OH, $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I as in Formula (VI); wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



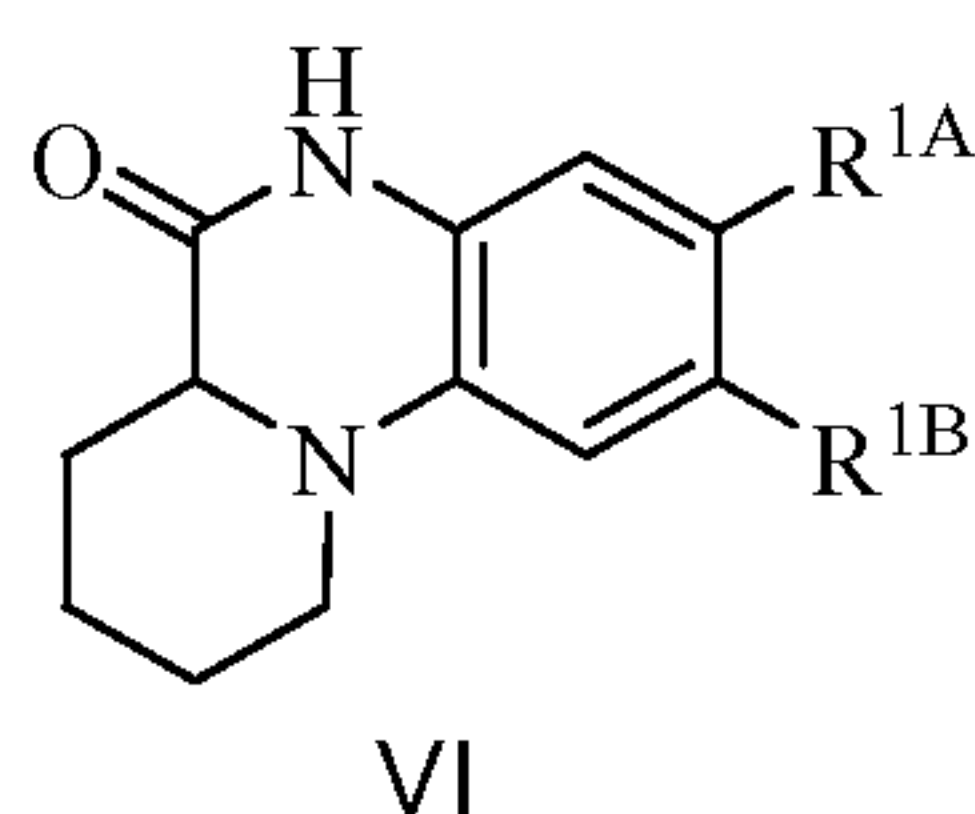
44. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the atoms to which they are attached are piperidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, or $NR^1C(O)R^1$ as in Formula (VI); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



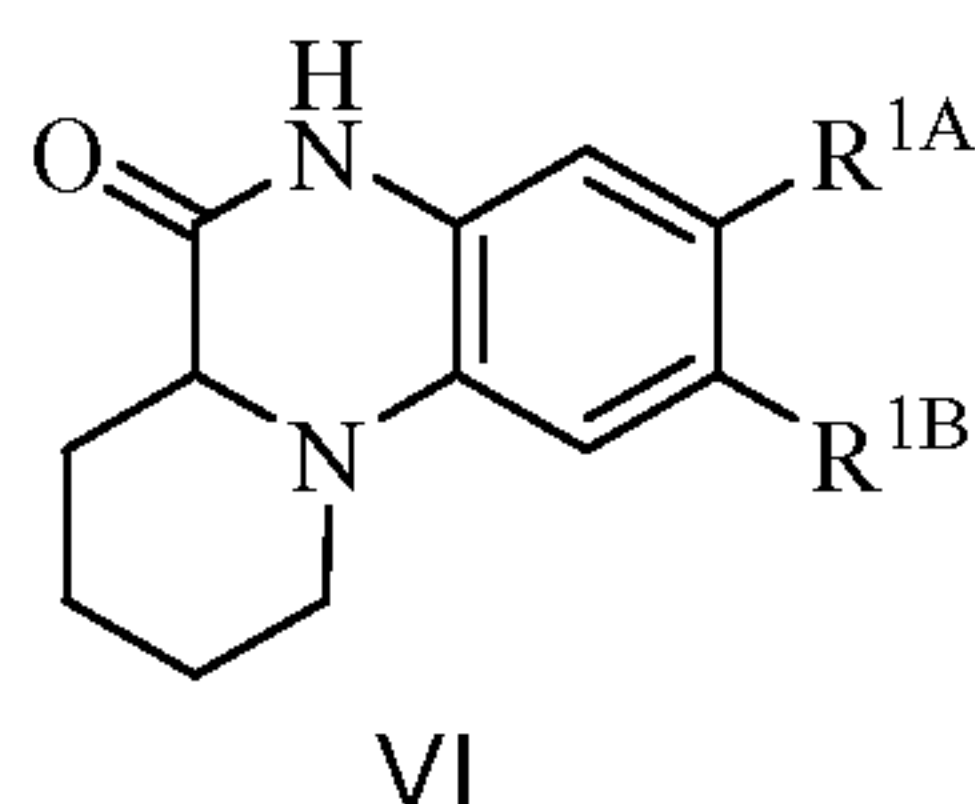
45. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are piperidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (VI); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



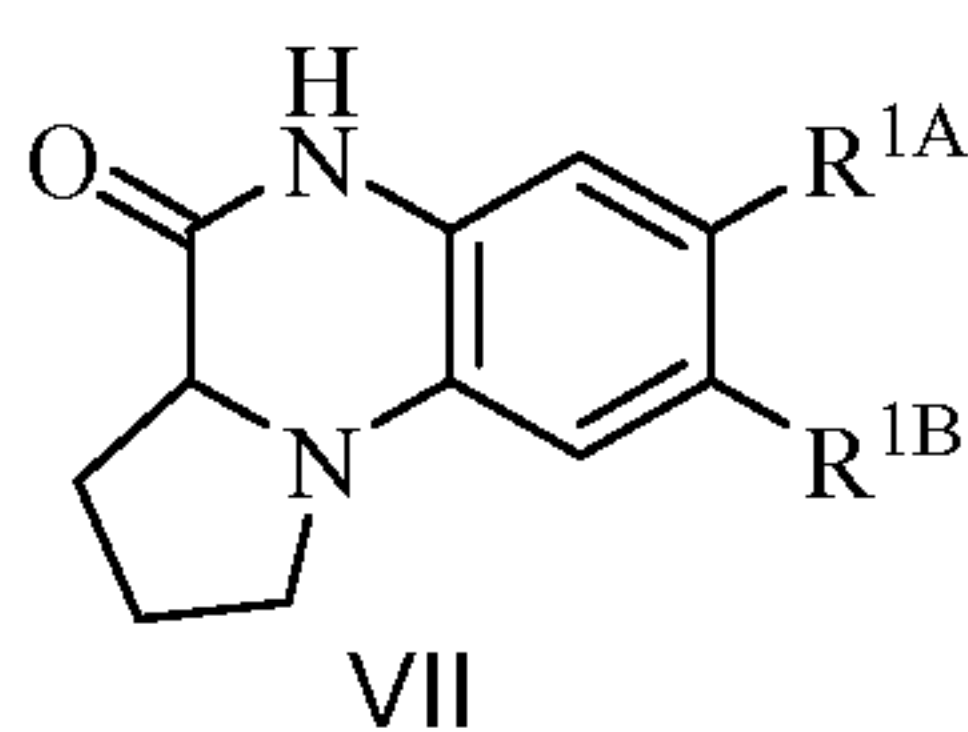
46. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are piperidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (VI); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹² is phenyl; R¹³ is heteroarene; R¹⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹⁶ is phenyl; R¹⁷ is heteroaryl; R¹⁸ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²¹ is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R²² is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²⁴ is phenyl; R²⁵ is heteroaryl; and R²⁶ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



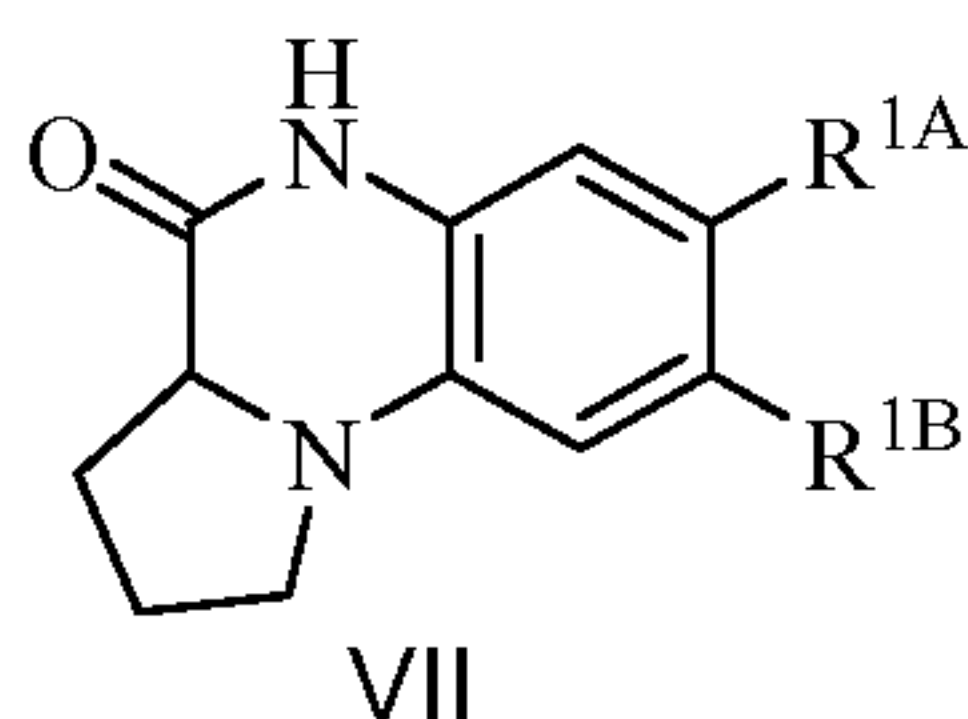
47. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are piperidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (VI); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, or heterocycloalkyl; R¹² is phenyl; R¹⁴ is cycloalkyl, or heterocycloalkyl; R¹⁸ is heterocycloalkyl; R²⁸ is phenyl; and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



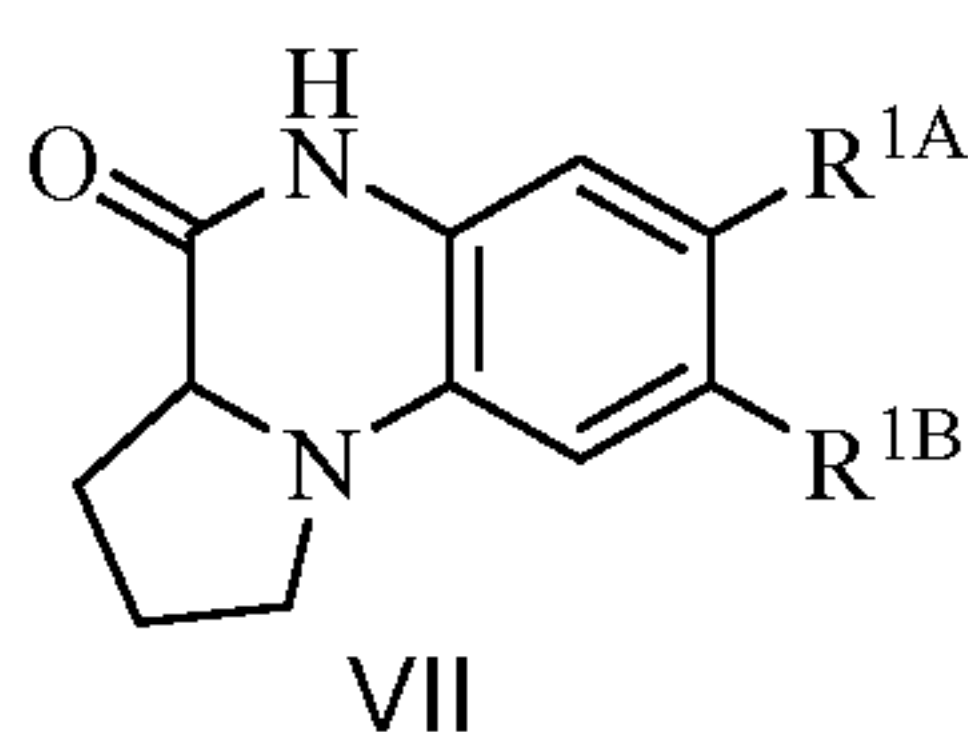
48. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are piperidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (VI); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl or heterocycloalkyl; R¹⁰ is alkyl which is unsubstituted or substituted with one or two of independently selected R¹¹, C(O)OH, N(R¹¹)₂, C(O)R¹¹, or C(O)OR¹¹; R¹¹ is R¹², R¹⁴ or R^{14A}; R¹² is phenyl; R¹⁴ is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R², R⁴, and R⁹ are independently unsubstituted independently substituted with R¹⁵, SO₂R¹⁵, NH₂, N(R¹⁵)₂, or (O); wherein R¹⁵ is R¹⁸ or R¹⁹; R¹⁸ is heterocycloalkyl; R¹⁹ is alkyl; wherein the moieties represented by R¹⁸ are independently unsubstituted or independently substituted with R²³; wherein R²³ is R²⁷; R²⁷ is alkyl each of which is substituted with R²⁸; and R²⁸ is phenyl.



49. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I as in Formula (VII); wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



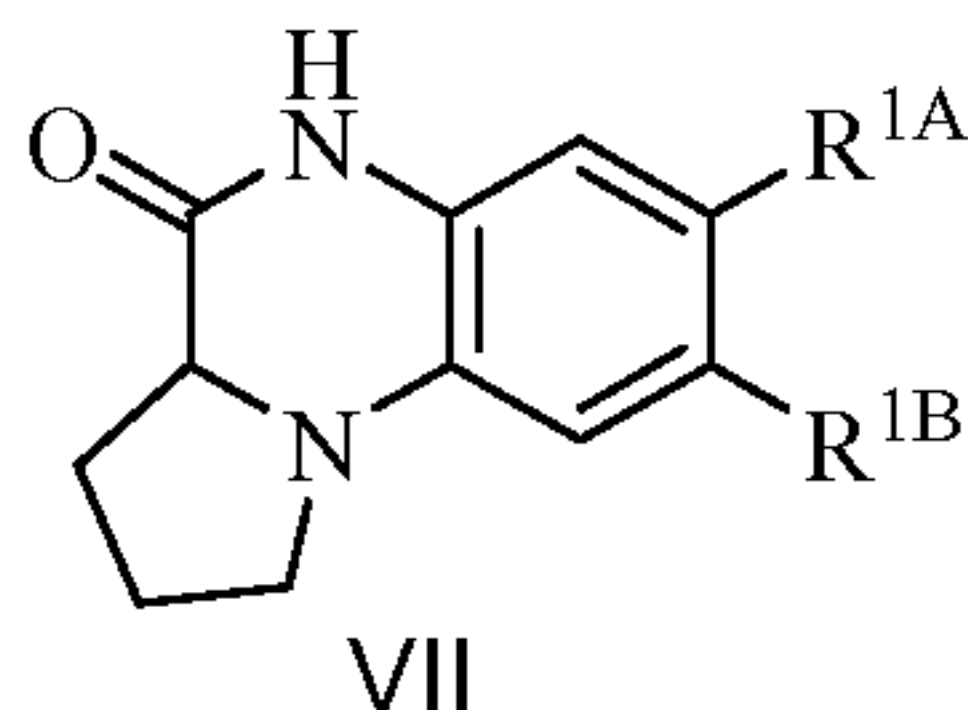
50. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, or NR¹C(O)R¹ as in Formula (VII); and wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



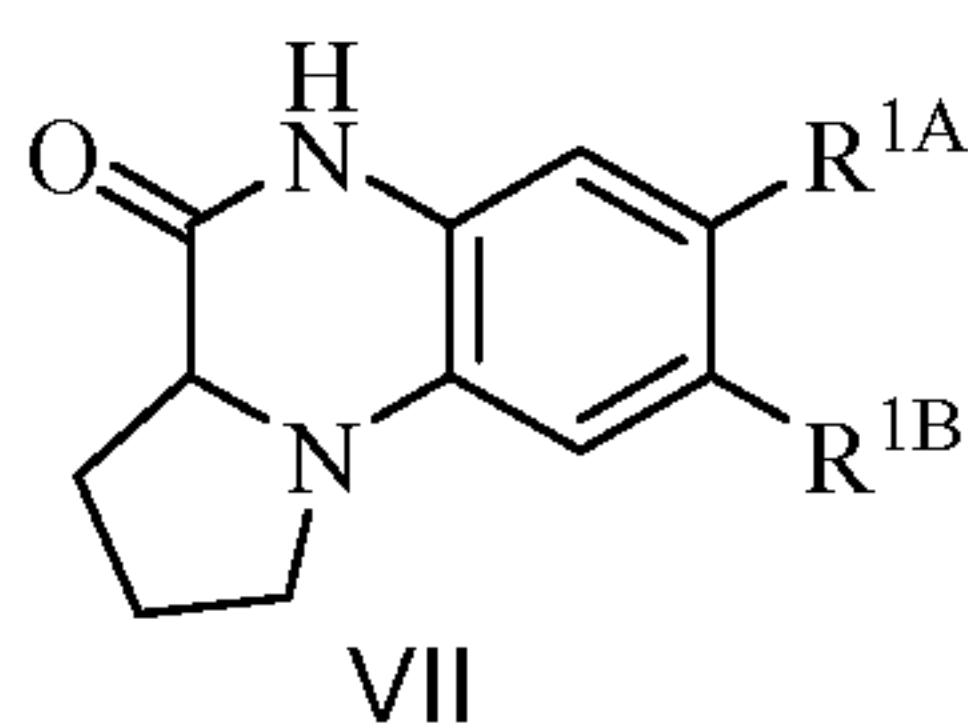
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51. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula

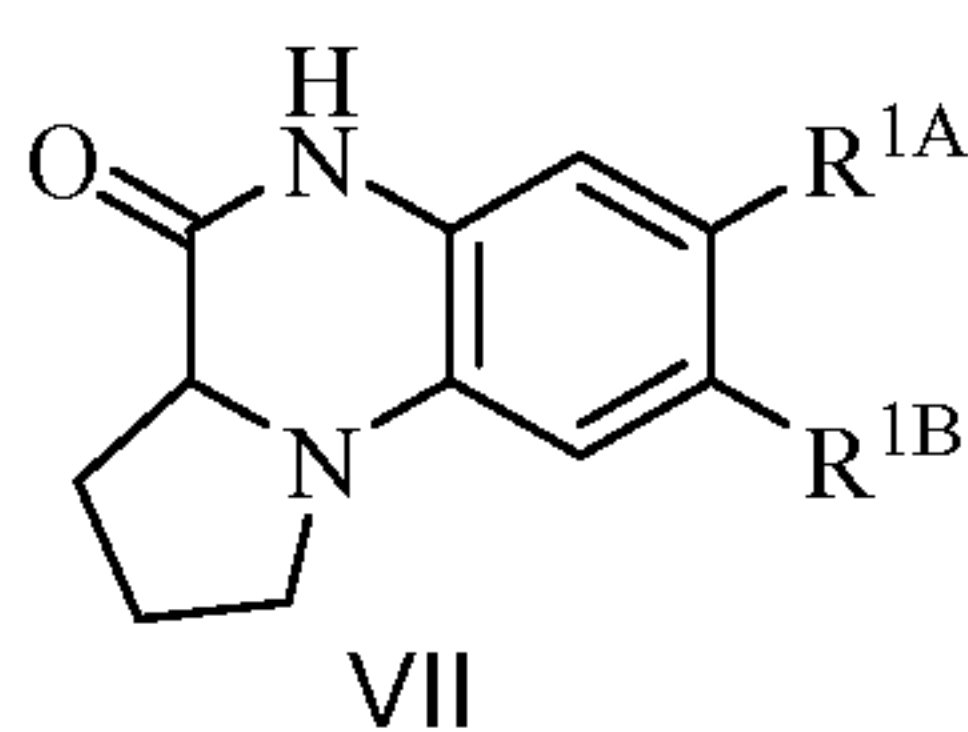
(VII); and wherein $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).



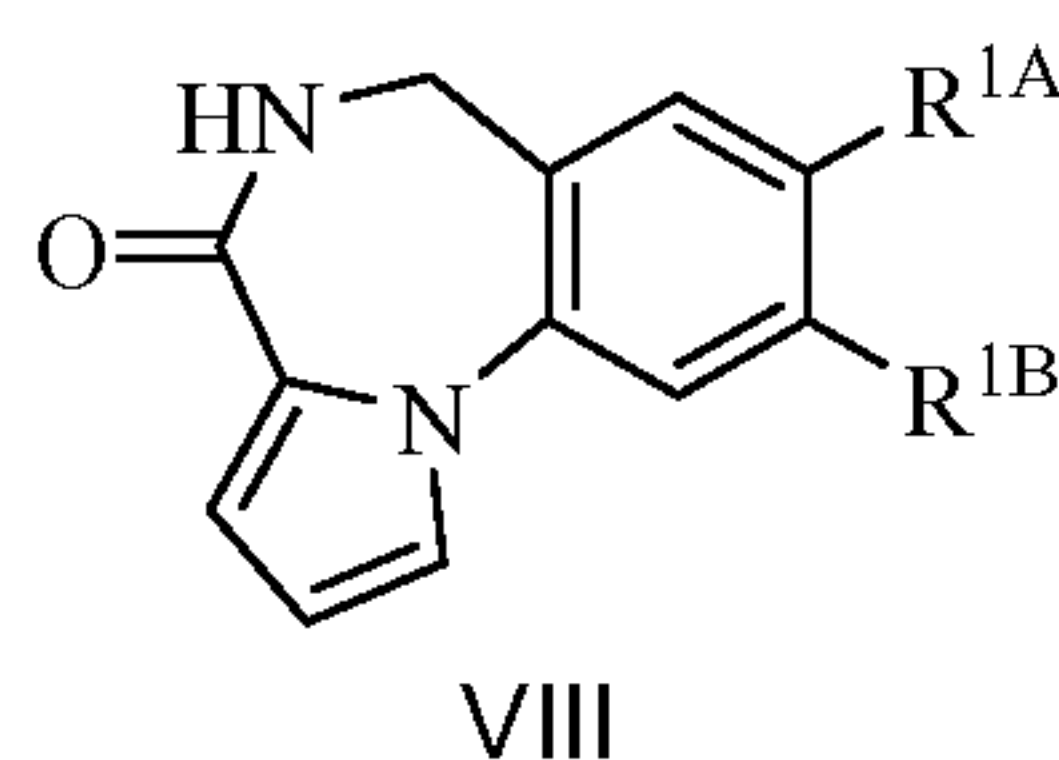
- 5 52. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the atoms to which they are attached are pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is $R^1, C(O)R^1, C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (VII); and R^1 is R^2, R^3, R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{12} is phenyl; R^{13} is heteroarene; R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{16} is phenyl; R^{17} is heteroaryl; R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein $R^5, R^6, R^{10}, R^{11}, R^{15}, R^{19}, R^{20}, R^{23}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).



- 20 53. In another embodiment of Formula (I), X is a bond, and A^1 and A^2 , together with the atoms to which they are attached are pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is $R^1, C(O)R^1, C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (VII); and R^1 is R^2, R^3, R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, or heterocycloalkyl; R^{12} is phenyl; R^{14} is cycloalkyl, or heterocycloalkyl; R^{18} is heterocycloalkyl; R^{28} is phenyl; and wherein $R^5, R^6, R^{10}, R^{11}, R^{15}, R^{19}, R^{20}, R^{23}, R^{27}, R^{28}, R^{29}$, and R^{30} are as described in Formula (I).

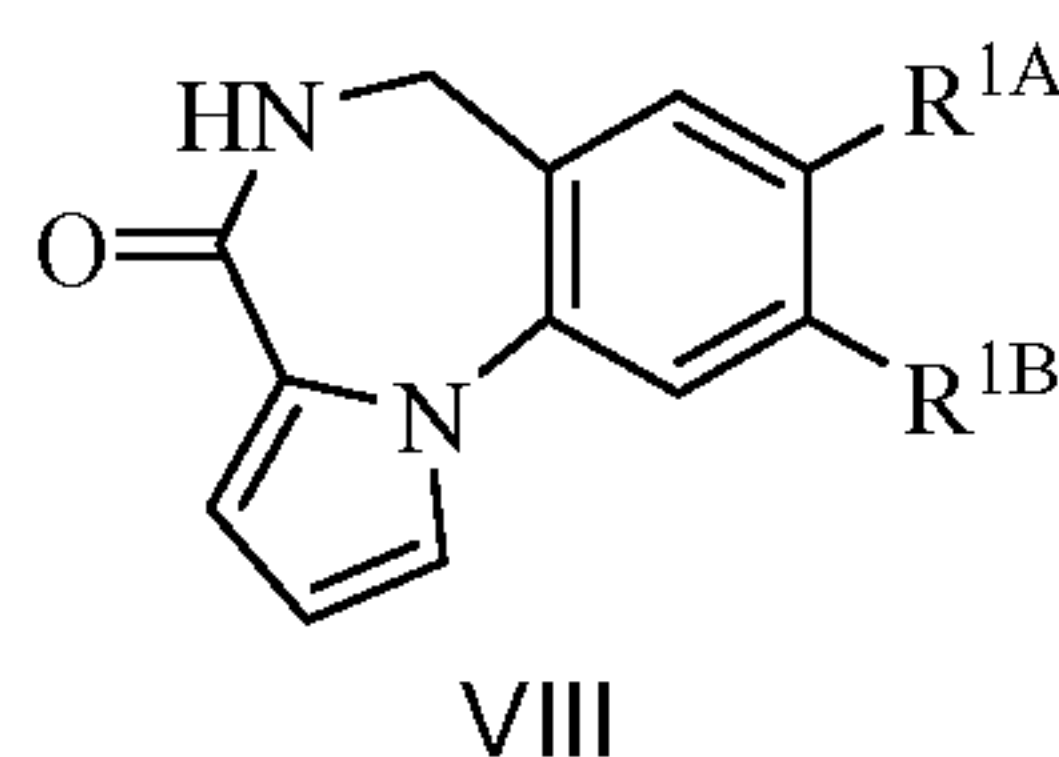


54. In another embodiment of Formula (I), X is a bond, and A¹ and A², together with the atoms to which they are attached are pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (VII); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl or heterocycloalkyl; R¹⁰ is alkyl which is unsubstituted or substituted with one or two of independently selected R¹¹, C(O)OH, N(R¹¹)₂, C(O)R¹¹, or C(O)OR¹¹; R¹¹ is R¹², R¹⁴ or R^{14A}; R¹² is phenyl; R¹⁴ is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R², R⁴, and R⁹ are independently unsubstituted or independently substituted with R¹⁵, SO₂R¹⁵, NH₂, N(R¹⁵)₂, or (O); wherein R¹⁵ is R¹⁸ or R¹⁹; R¹⁸ is heterocycloalkyl; R¹⁹ is alkyl; wherein the moieties represented by R¹⁸ are independently unsubstituted or independently substituted with R²³; wherein R²³ is R²⁷; R²⁷ is alkyl each of which is substituted with R²⁸; and R²⁸ is phenyl.

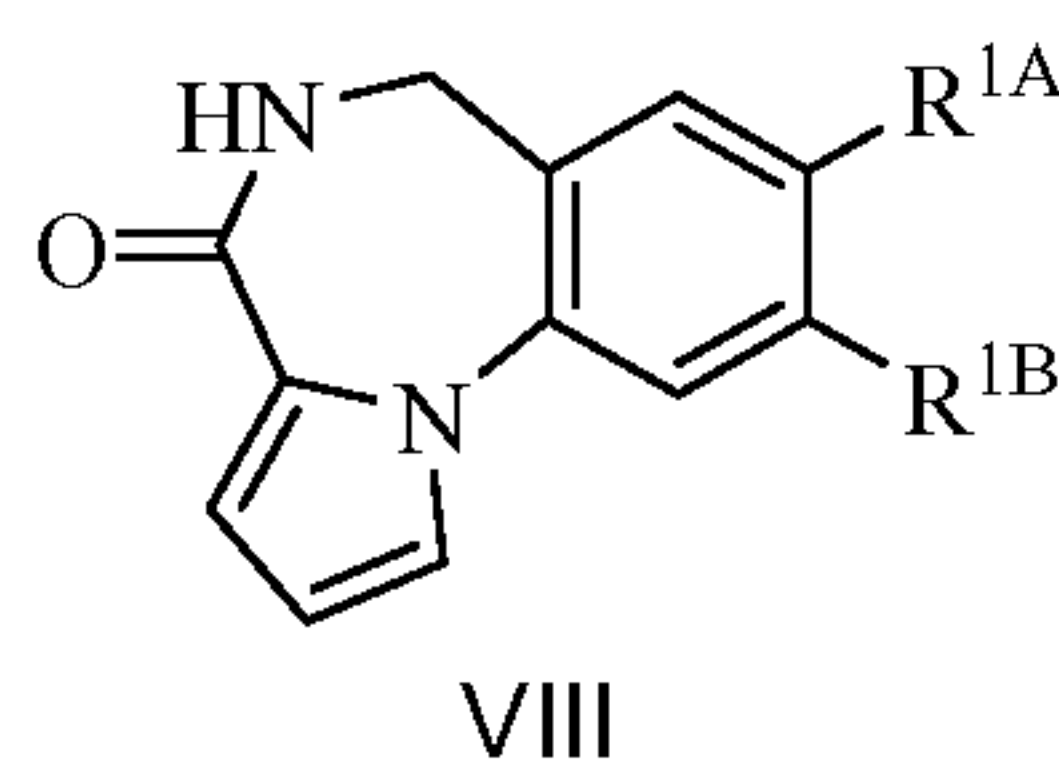


55. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are pyrrole; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I as in Formula (VIII); wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵,

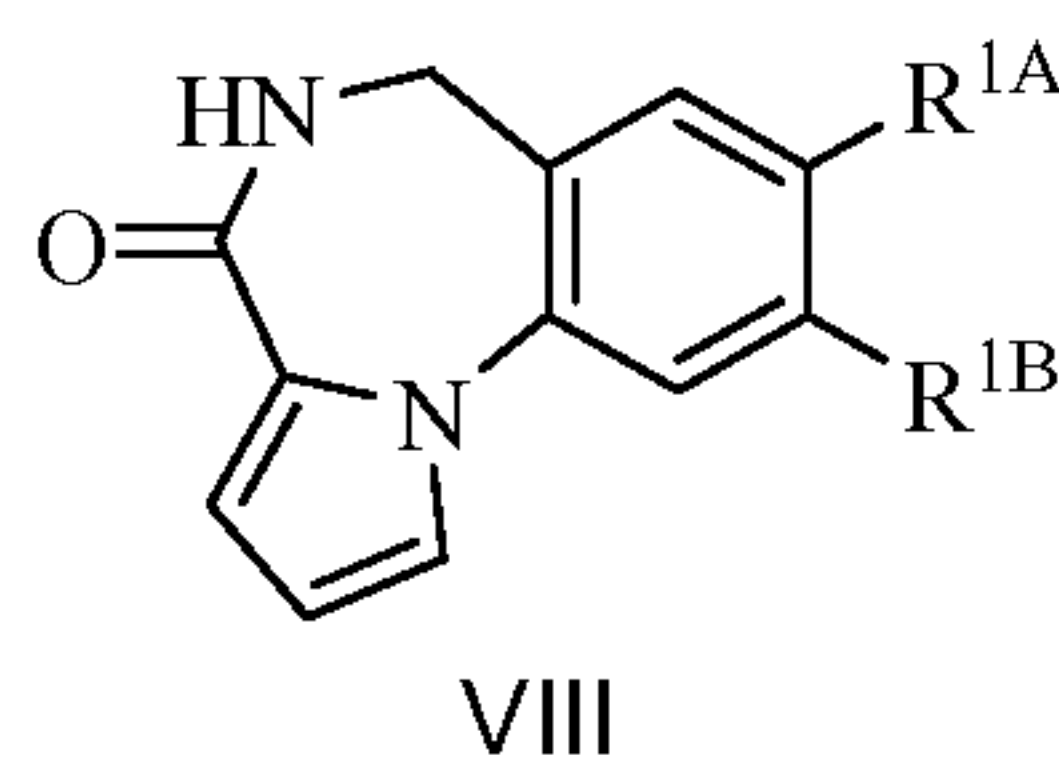
R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



56. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the
 5 atoms to which they are attached are pyrrole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, or $NR^1C(O)R^1$ as in Formula (VIII); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} ,
 10 R^{28} , R^{29} , and R^{30} are as described in Formula (I).

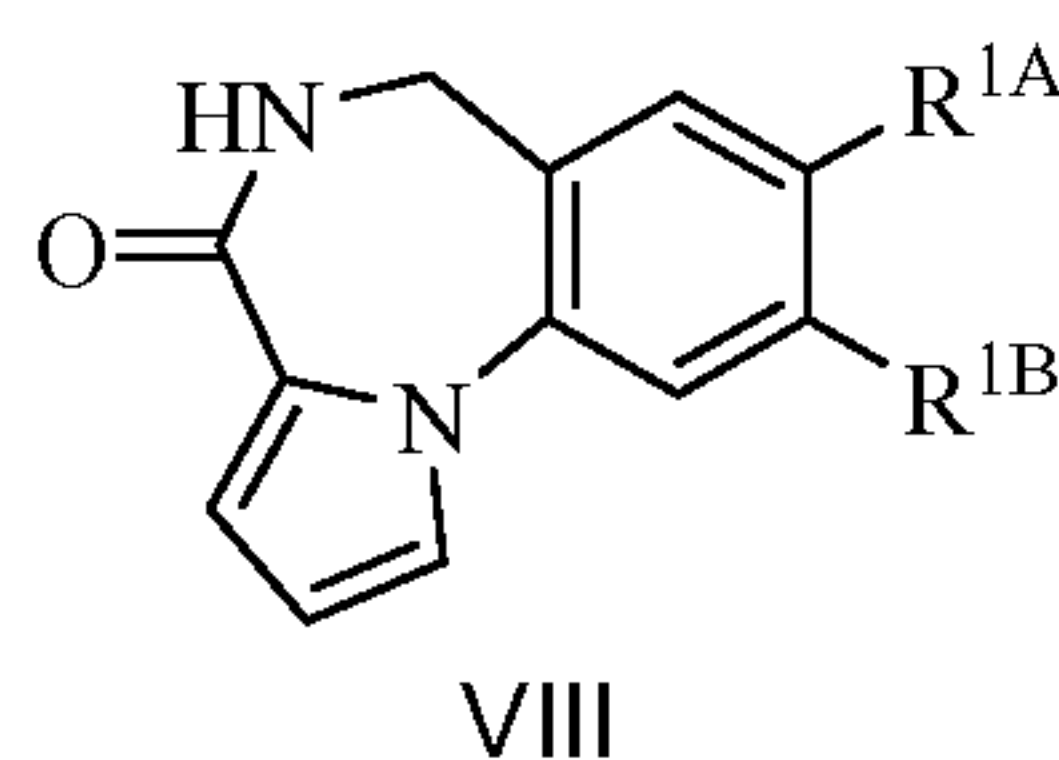


57. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the
 atoms to which they are attached are pyrrole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and
 15 R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (VIII); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

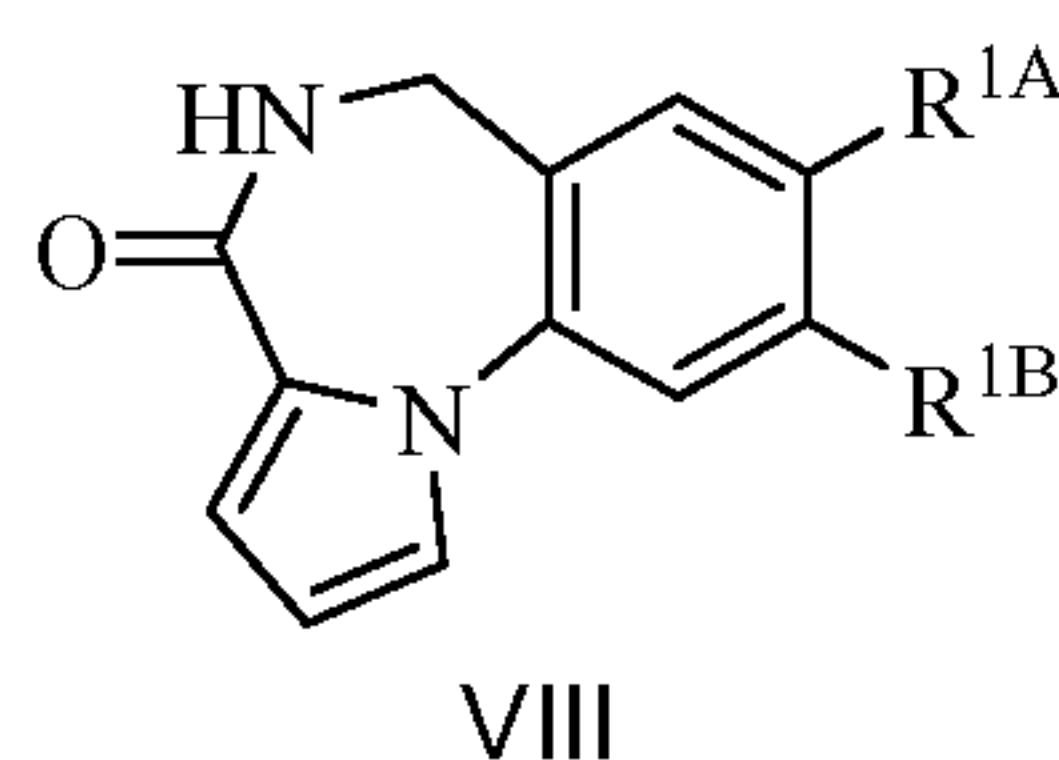


58. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the
 20 atoms to which they are attached are pyrrole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (VIII); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^7 is phenyl; R^8 is heteroarene; R^9 is

- cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{12} is phenyl; R^{13} is heteroarene; R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{16} is phenyl; R^{17} is heteroaryl; R^{18} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

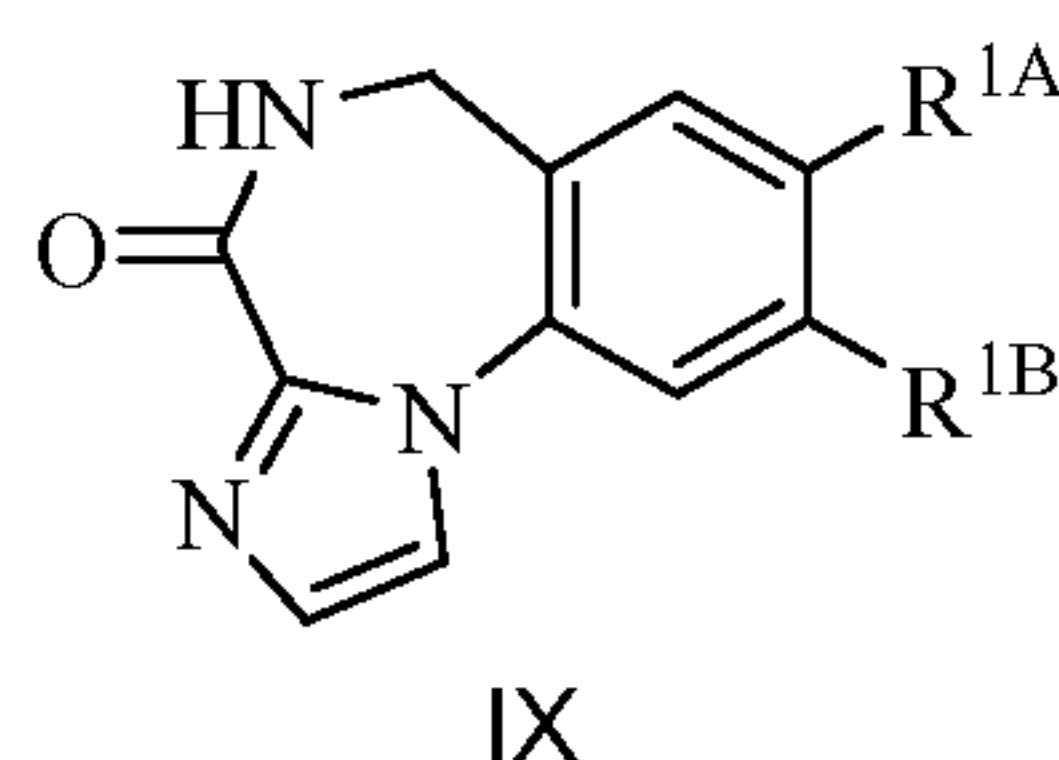


59. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (VIII); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, or heterocycloalkyl; R^{12} is phenyl; R^{14} is cycloalkyl, or heterocycloalkyl; R^{18} is heterocycloalkyl; R^{28} is phenyl; and wherein R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

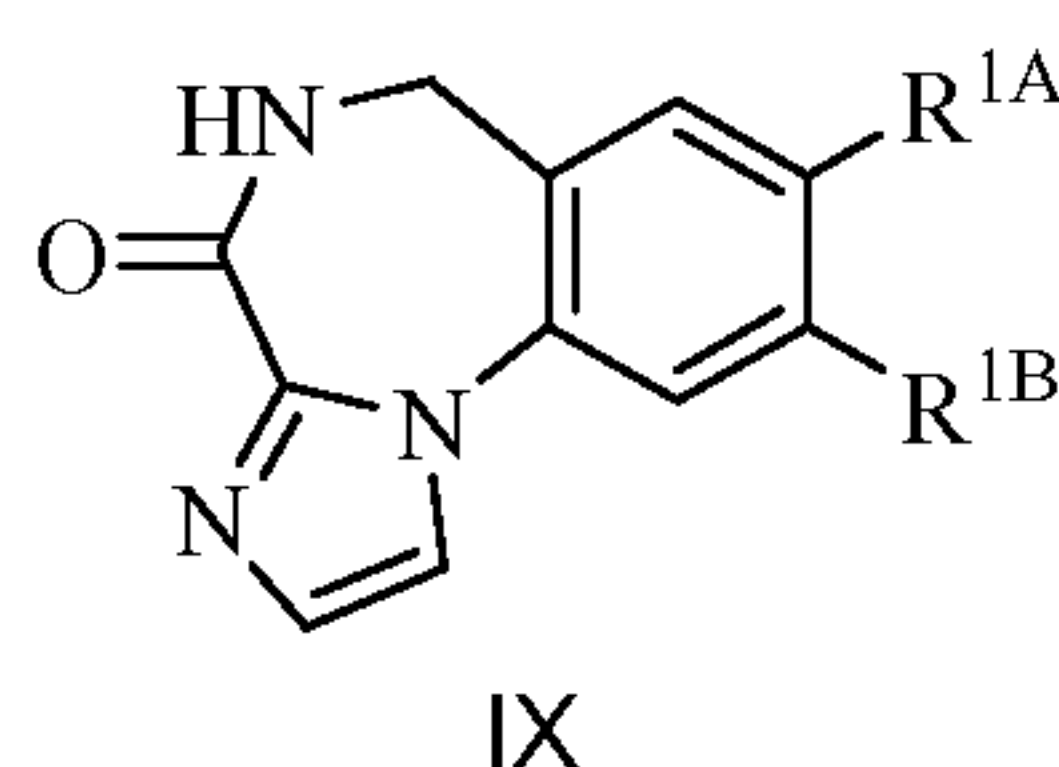


60. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (VIII); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^5 is alkyl which is unsubstituted or substituted with one or two of independently selected R^6 , NHR^6 , $N(R^6)_2$, $C(O)R^6$, $NR^6C(O)R^6$, or $NR^6S(O)_2R^6$; R^6 is R^7 , R^8 , R^9 or R^{10} ; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl or heterocycloalkyl; R^{10} is

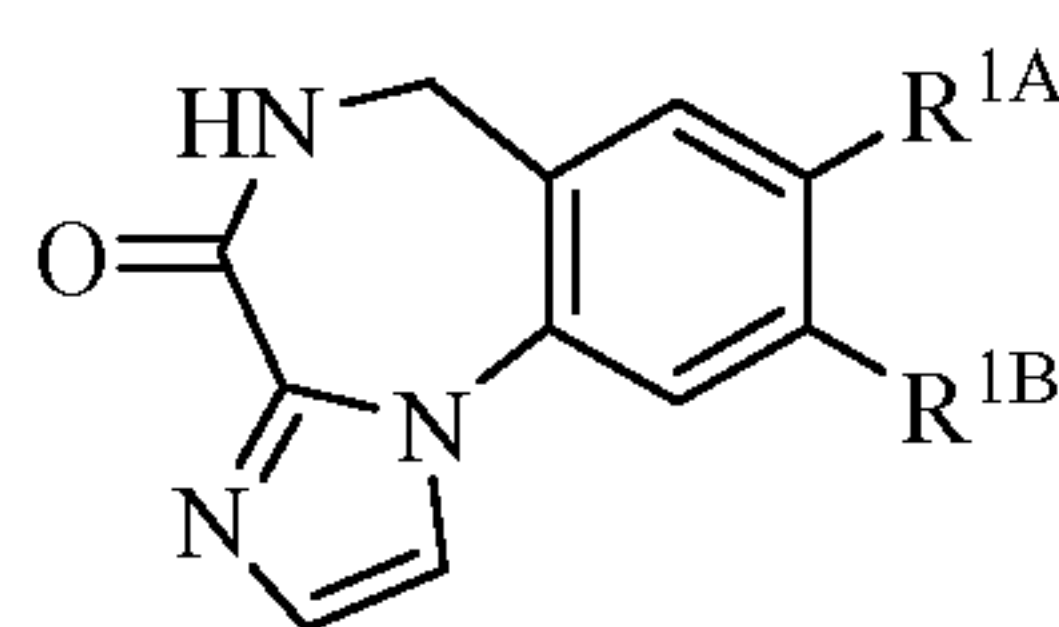
- alkyl which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, $N(R^{11})_2$, $C(O)R^{11}$, or $C(O)OR^{11}$; R^{11} is R^{12} , R^{14} or R^{14A} ; R^{12} is phenyl; R^{14} is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R^2 , R^4 , and R^9 are independently unsubstituted independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$, or (O) ; wherein R^{15} is R^{18} or R^{19} ; R^{18} is heterocycloalkyl; R^{19} is alkyl; wherein the moieties represented by R^{18} are independently unsubstituted or independently substituted with R^{23} ; wherein R^{23} is R^{27} ; R^{27} is alkyl each of which is substituted with R^{28} ; and R^{28} is phenyl.



61. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are imidazole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $S(O)R^1$, SO_2R^1 , NH_2 , NHR^1 , $N(R^1)_2$, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHC(O)NH_2$, $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, OH , $C(O)OH$, CN , CF_3 , OCF_3 , CF_2CF_3 , F , Cl , Br or I as in Formula (IX); wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

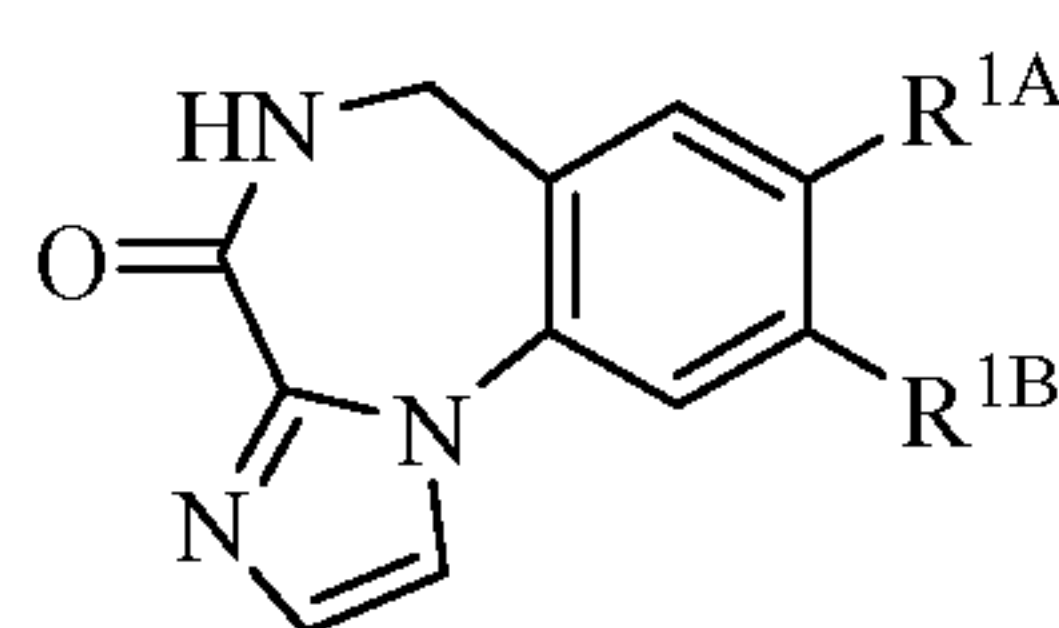


62. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are imidazole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, or $NR^1C(O)R^1$ as in Formula (IX); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



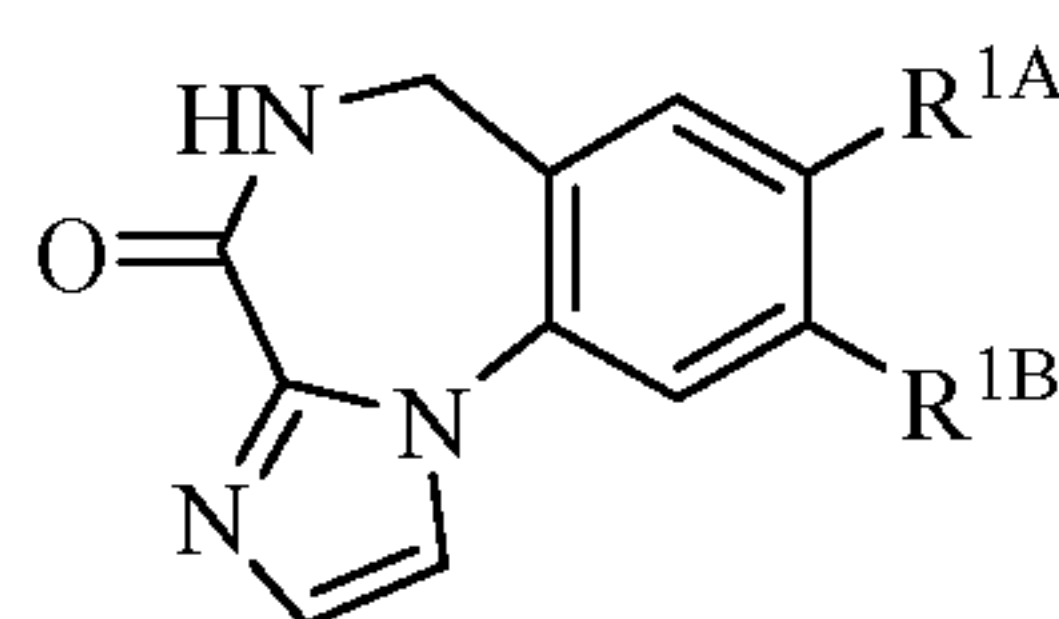
IX

63. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are imidazole; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (IX); and wherein R¹, R², R³, R⁴,
 5 R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



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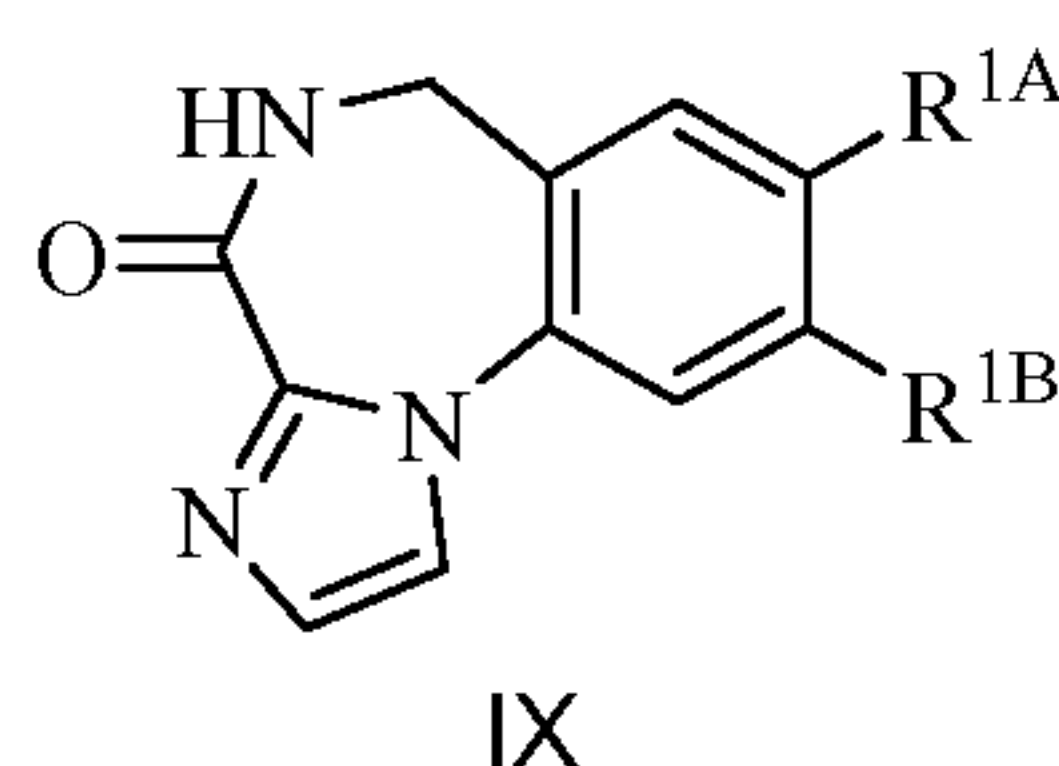
64. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to
 10 which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (IX); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹² is
 15 phenyl; R¹³ is heteroarene; R¹⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹⁶ is phenyl; R¹⁷ is heteroaryl; R¹⁸ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²¹ is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R²² is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²⁴ is phenyl; R²⁵ is heteroaryl; and
 20 R²⁶ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



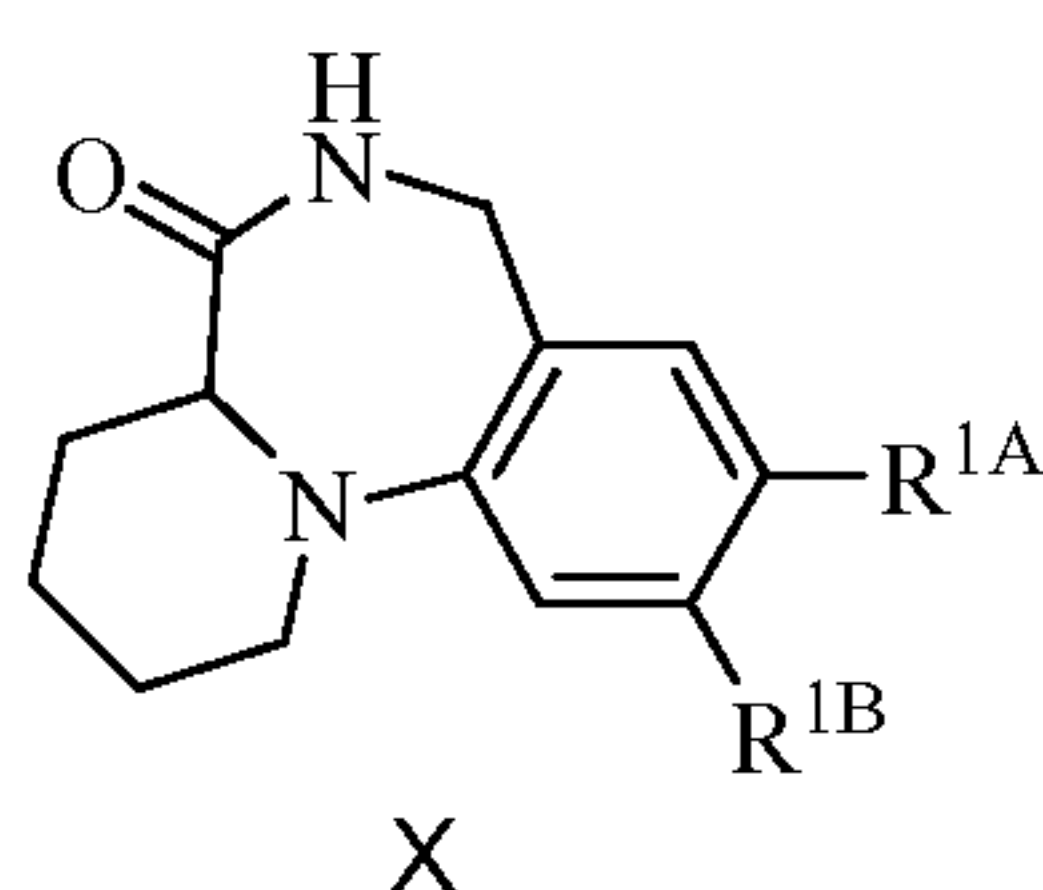
IX

65. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are imidazole; A³ and A⁴, together with the atoms to

which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (IX); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, or heterocycloalkyl; R^{12} is phenyl; R^{14} is cycloalkyl, or heterocycloalkyl; R^{18} is heterocycloalkyl; R^{28} is phenyl; and wherein R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

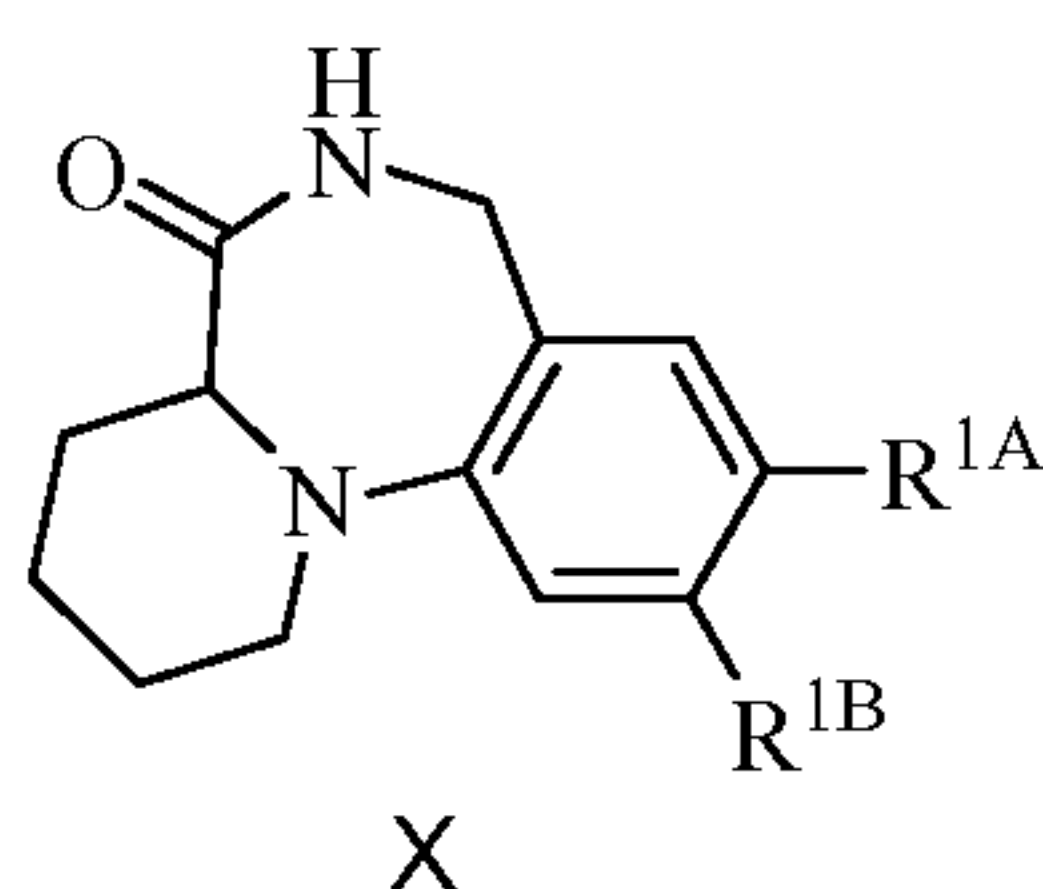


66. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are imidazole; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (IX); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^5 is alkyl which is unsubstituted or substituted with one or two of independently selected R^6 , NHR^6 , $N(R^6)_2$, $C(O)R^6$, $NR^6C(O)R^6$, or $NR^6S(O)_2R^6$; R^6 is R^7 , R^8 , R^9 or R^{10} ; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl or heterocycloalkyl; R^{10} is alkyl which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, $N(R^{11})_2$, $C(O)R^{11}$, or $C(O)OR^{11}$; R^{11} is R^{12} , R^{14} or R^{14A} ; R^{12} is phenyl; R^{14} is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R^2 , R^4 , and R^9 are independently unsubstituted or independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$, or (O); wherein R^{15} is R^{18} or R^{19} ; R^{18} is heterocycloalkyl; R^{19} is alkyl; wherein the moieties represented by R^{18} are independently unsubstituted or independently substituted with R^{23} ; wherein R^{23} is R^{27} ; R^{27} is alkyl each of which is substituted with R^{28} ; and R^{28} is phenyl.

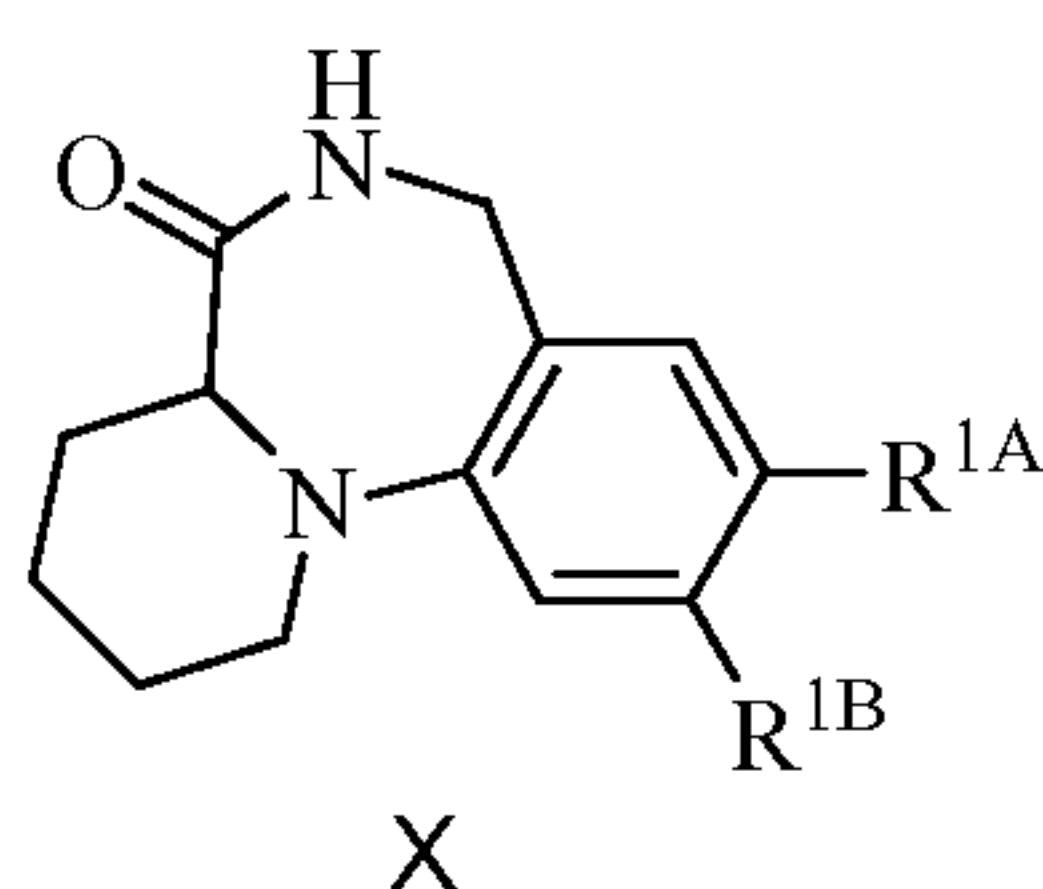


67. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are piperidine; A^3 and A^4 , together with the atoms to

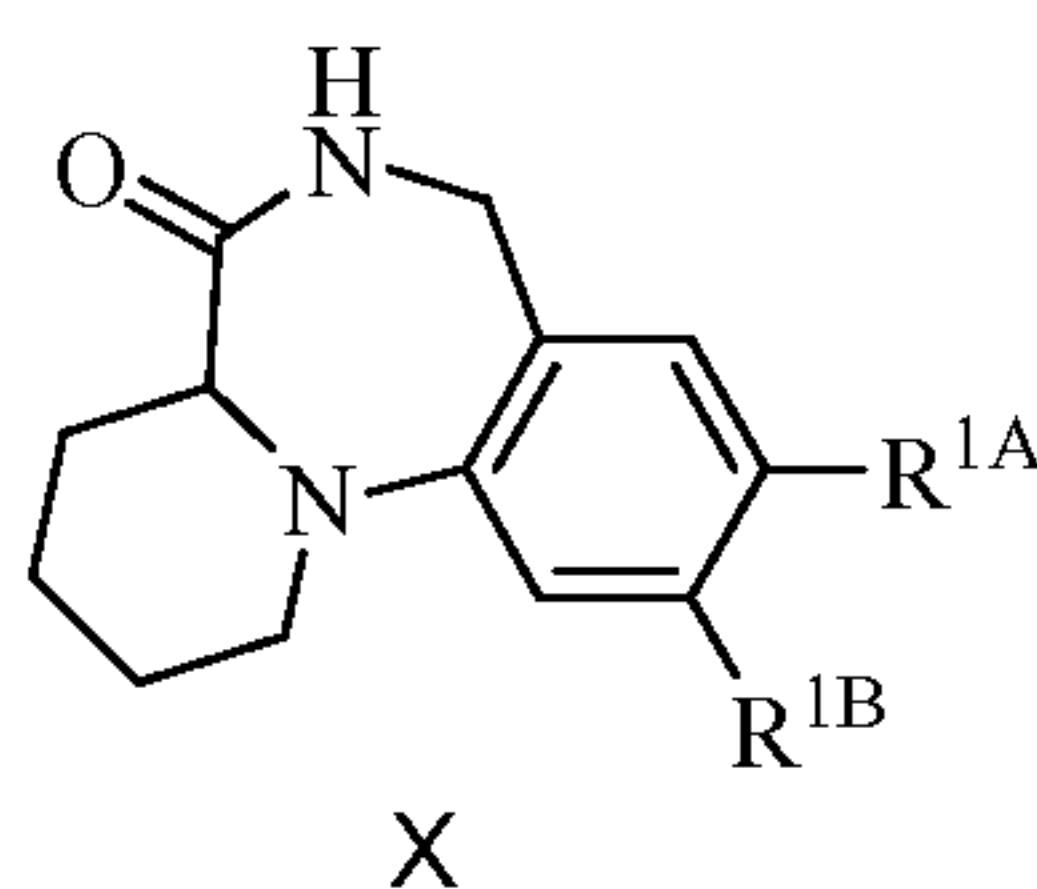
which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $S(O)R^1$, SO_2R^1 , NH_2 , NHR^1 , $N(R^1)_2$, $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, $NR^1C(O)R^1$, $NHSO_2R^1$, $NR^1SO_2R^1$, $NHC(O)OR^1$, $NR^1C(O)OR^1$, SO_2NH_2 , SO_2NHR^1 , $SO_2N(R^1)_2$, $NHC(O)NH_2$,
 5 $NHC(O)NHR^1$, $NHC(O)N(R^1)_2$, OH, $C(O)OH$, CN, CF_3 , OCF_3 , CF_2CF_3 , F, Cl, Br or I as in Formula (X); wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



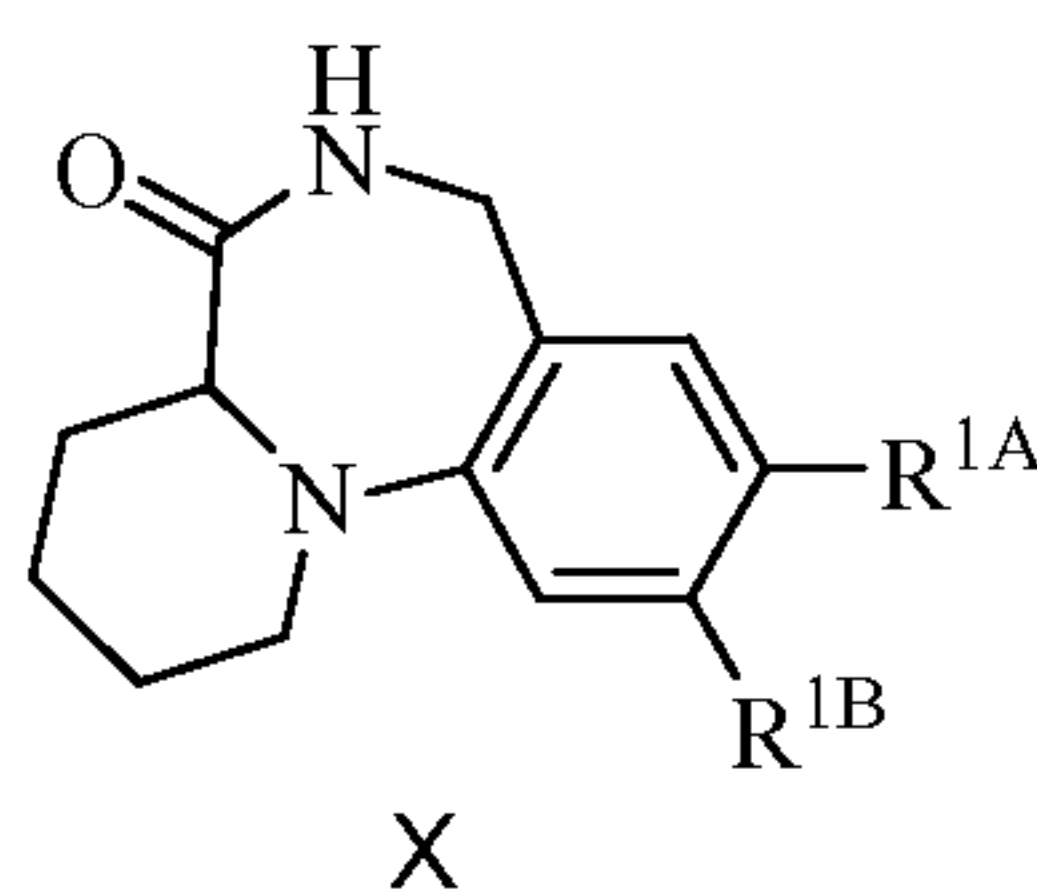
10 68. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are piperidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, or $NR^1C(O)R^1$ as in Formula (X); and wherein R^1 , R^2 , R^3 , R^4 ,
 15 R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



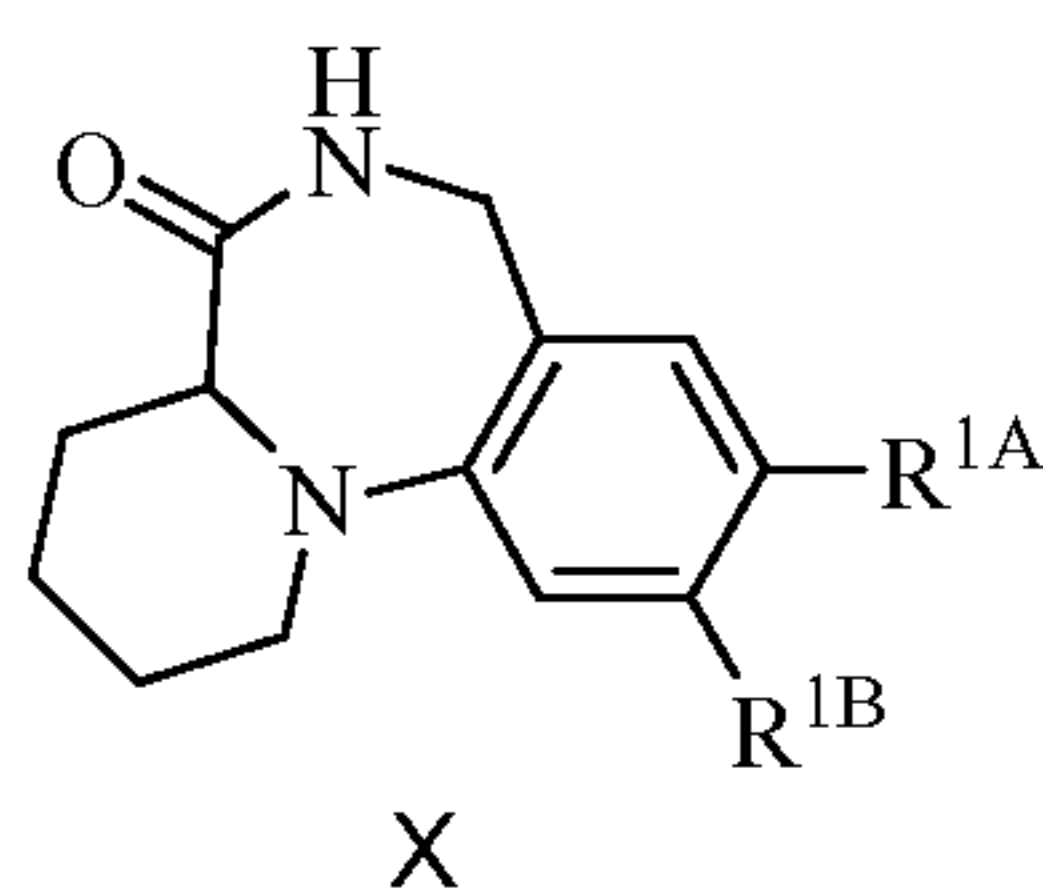
69. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are piperidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (X); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



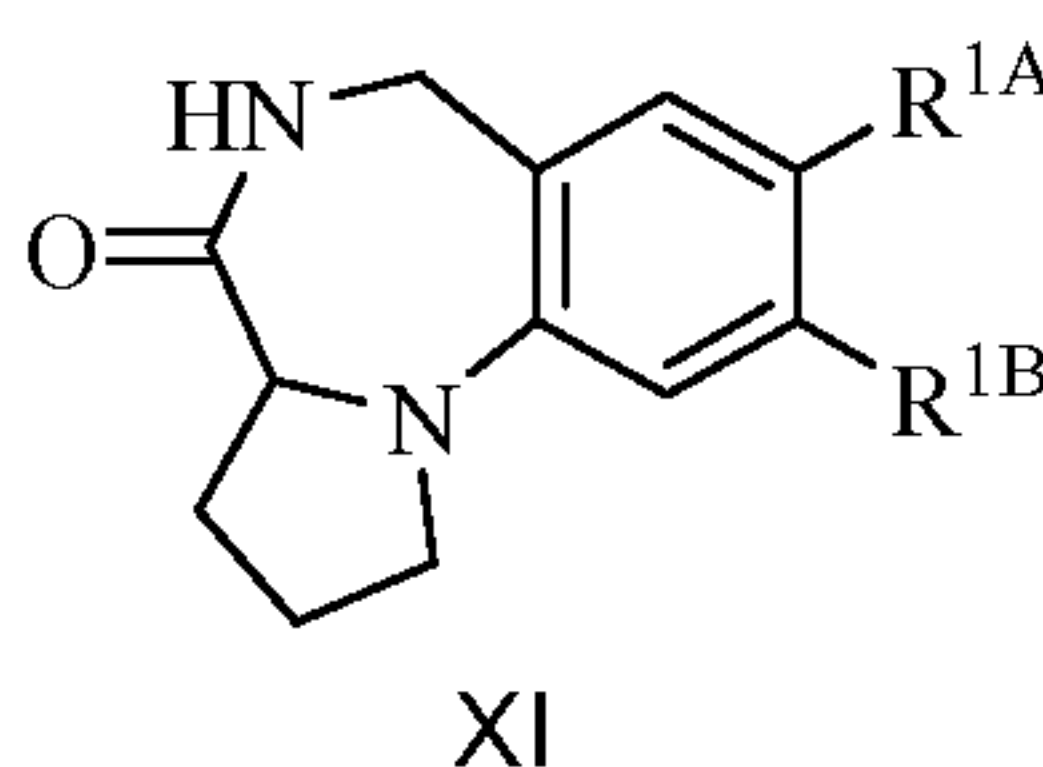
70. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are piperidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (X); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹² is phenyl; R¹³ is heteroarene; R¹⁴ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R¹⁶ is phenyl; R¹⁷ is heteroaryl; R¹⁸ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²¹ is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R²² is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R²⁴ is phenyl; R²⁵ is heteroaryl; and R²⁶ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).



71. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are piperidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (X); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl, or heterocycloalkyl; R¹² is phenyl; R¹⁴ is cycloalkyl, or heterocycloalkyl; R¹⁸ is heterocycloalkyl; R²⁸ is phenyl; and wherein R⁵, R⁶, R¹⁰, R¹¹, R¹⁵, R¹⁹, R²⁰, R²³, R²⁷, R²⁸, R²⁹, and R³⁰ are as described in Formula (I).

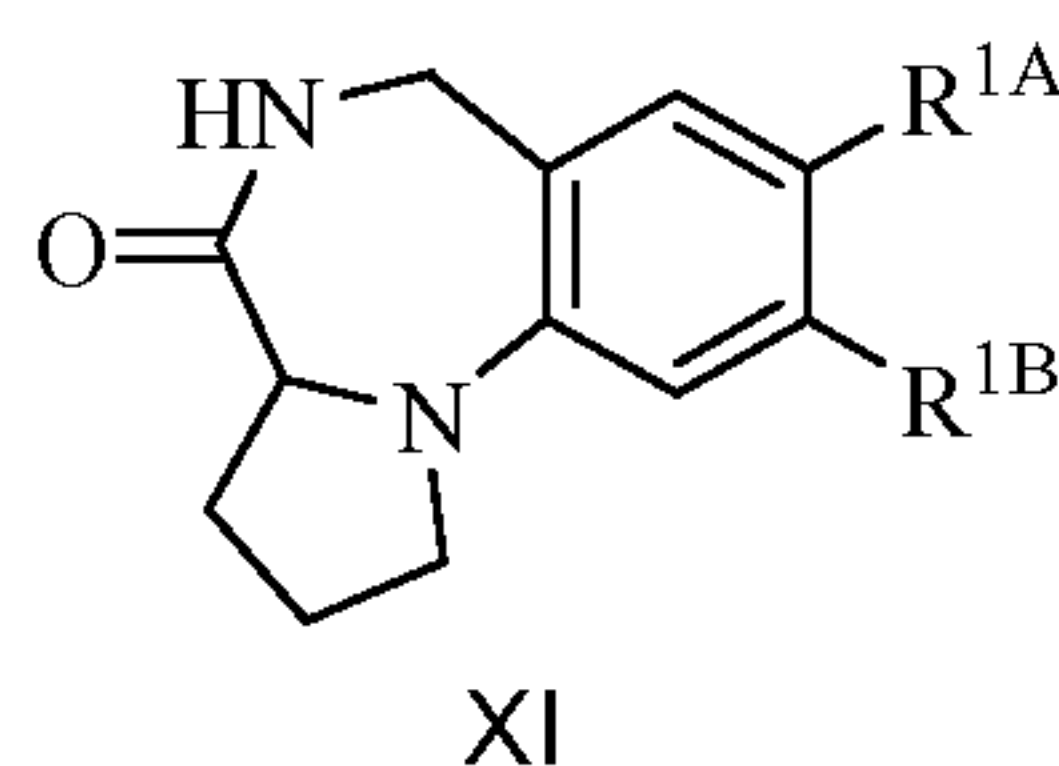


72. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are piperidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂ as in Formula (X); and R¹ is R², R³, R⁴ or R⁵; R² is phenyl; R³ is heteroarene; R⁴ is cycloalkyl or heterocycloalkyl; R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, NR⁶C(O)R⁶, or NR⁶S(O)₂R⁶; R⁶ is R⁷, R⁸, R⁹ or R¹⁰; R⁷ is phenyl; R⁸ is heteroarene; R⁹ is cycloalkyl or heterocycloalkyl; R¹⁰ is alkyl which is unsubstituted or substituted with one or two of independently selected R¹¹, C(O)OH, N(R¹¹)₂, C(O)R¹¹, or C(O)OR¹¹; R¹¹ is R¹², R¹⁴ or R^{14A}; R¹² is phenyl; R¹⁴ is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R², R⁴, and R⁹ are independently unsubstituted independently substituted with R¹⁵, SO₂R¹⁵, NH₂, N(R¹⁵)₂, or (O); wherein R¹⁵ is R¹⁸ or R¹⁹; R¹⁸ is heterocycloalkyl; R¹⁹ is alkyl; wherein the moieties represented by R¹⁸ are independently unsubstituted or independently substituted with R²³; wherein R²³ is R²⁷; R²⁷ is alkyl each of which is substituted with R²⁸; and R²⁸ is phenyl.

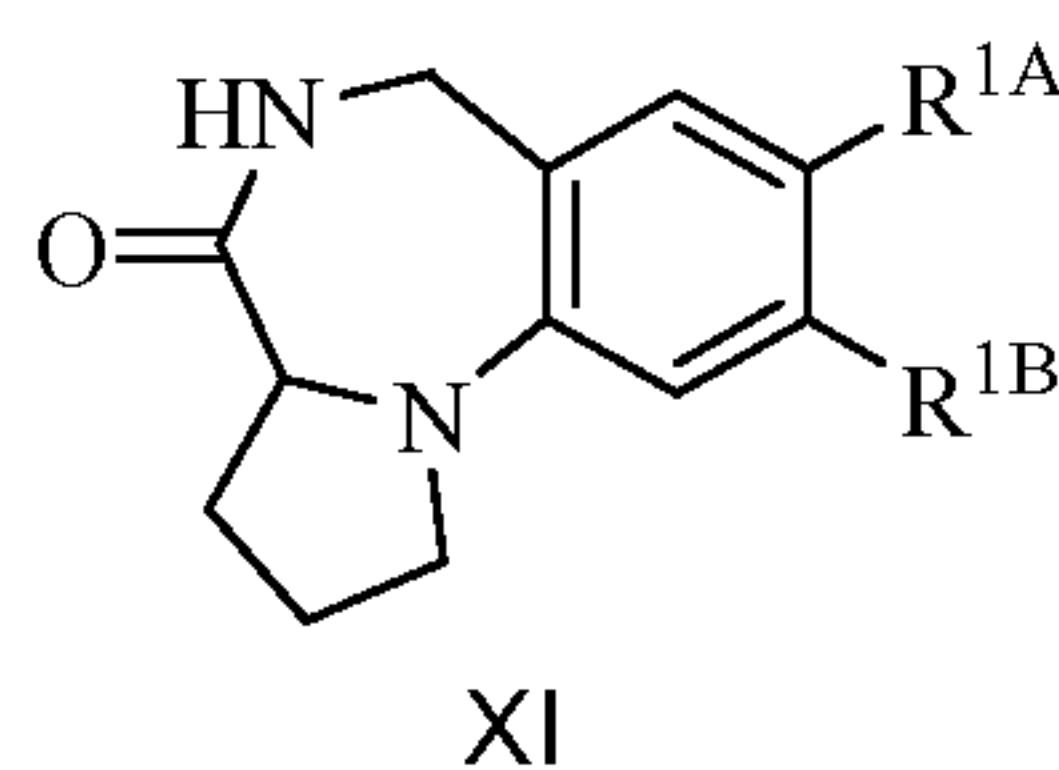


73. In another embodiment of Formula (I), X is a CH₂, and A¹ and A², together with the atoms to which they are attached are pyrrolidine; A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B}; and one of R^{1A} and R^{1B} is H, and the other is R¹, OR¹, SR¹, S(O)R¹, SO₂R¹, NH₂, NHR¹, N(R¹)₂, C(O)R¹, C(O)NH₂, C(O)NHR¹, C(O)N(R¹)₂, NHC(O)R¹, NR¹C(O)R¹, NHSO₂R¹, NR¹SO₂R¹, NHC(O)OR¹, NR¹C(O)OR¹, SO₂NH₂, SO₂NHR¹, SO₂N(R¹)₂, NHC(O)NH₂, NHC(O)NHR¹, NHC(O)N(R¹)₂, OH, C(O)OH, CN, CF₃, OCF₃, CF₂CF₃, F, Cl, Br or I as in Formula (XI); wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵,

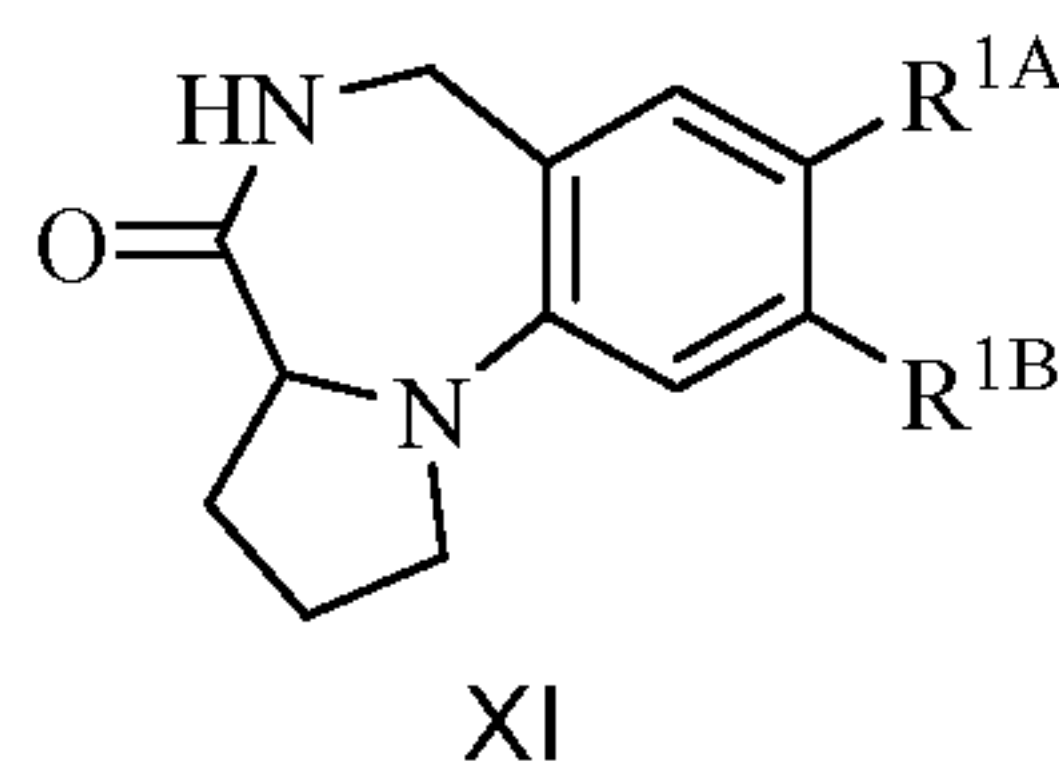
R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



74. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , OR^1 , SR^1 , $C(O)R^1$, $C(O)NH_2$, $C(O)NHR^1$, $C(O)N(R^1)_2$, $NHC(O)R^1$, or $NR^1C(O)R^1$ as in Formula (XI); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



75. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (XI); and wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



76. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula (XI); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl,

cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^7 is phenyl; R^8 is heteroarene;

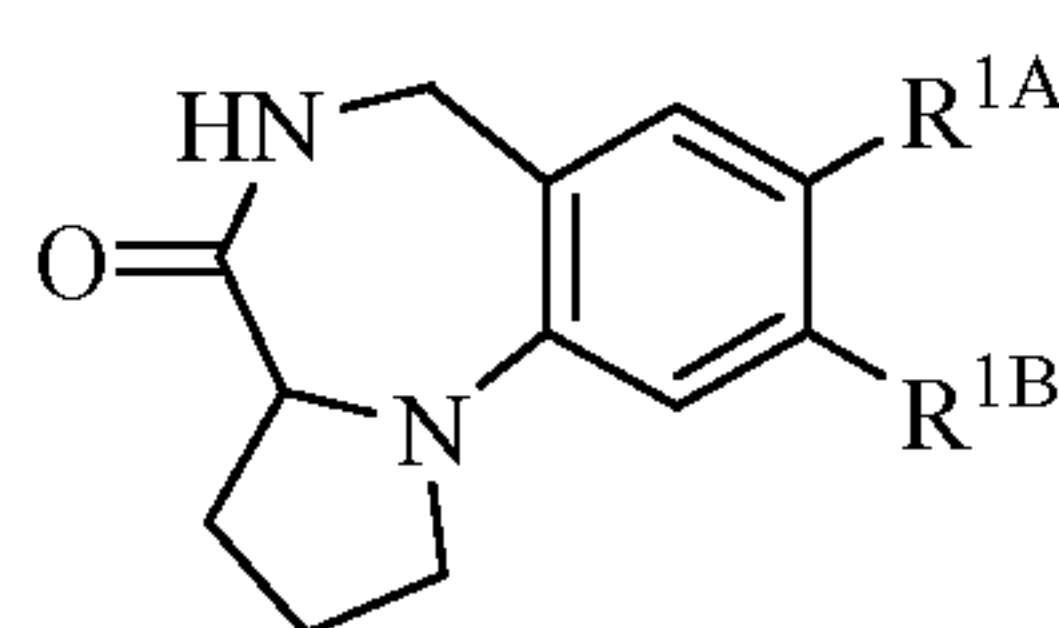
R^9 is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{12} is phenyl; R^{13} is heteroarene; R^{14} is cycloalkyl, cycloalkenyl, heterocycloalkyl or

heterocycloalkenyl; R^{16} is phenyl; R^{17} is heteroaryl; R^{18} is cycloalkyl, cycloalkenyl,

5 heterocycloalkyl or heterocycloalkenyl; R^{21} is phenyl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; R^{22} is phenyl, heteroaryl, cycloalkyl,

cycloalkenyl, heterocycloalkyl or heterocycloalkenyl; R^{24} is phenyl; R^{25} is heteroaryl; and

R^{26} is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, and wherein R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).

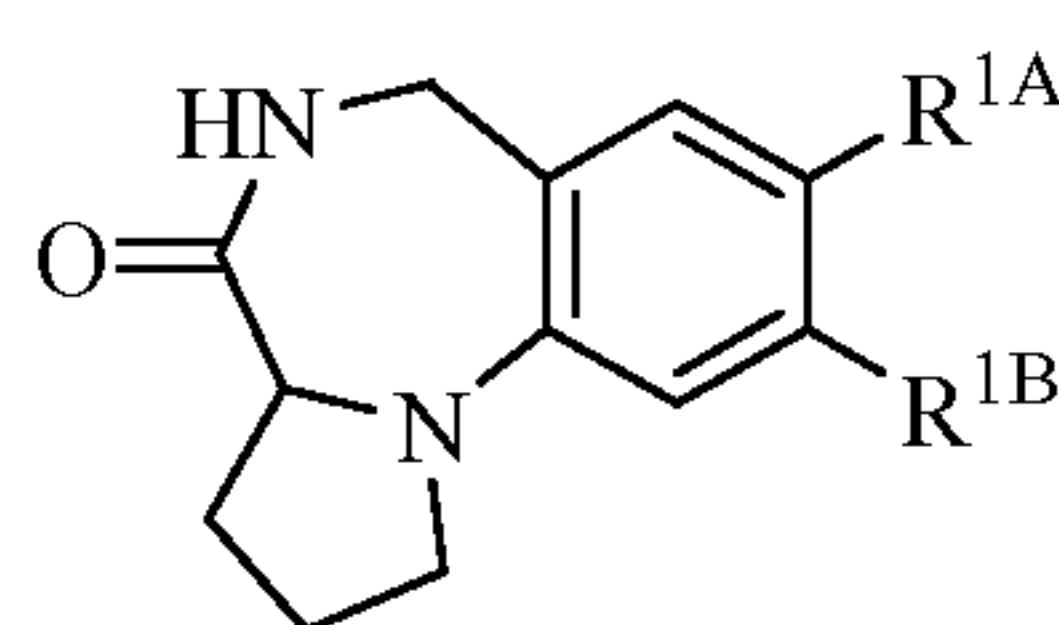


XI

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77. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula

15 (XI); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl, or heterocycloalkyl; R^{12} is phenyl; R^{14} is cycloalkyl, or heterocycloalkyl; R^{18} is heterocycloalkyl; R^{28} is phenyl; and wherein R^5 , R^6 , R^{10} , R^{11} , R^{15} , R^{19} , R^{20} , R^{23} , R^{27} , R^{28} , R^{29} , and R^{30} are as described in Formula (I).



XI

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78. In another embodiment of Formula (I), X is a CH_2 , and A^1 and A^2 , together with the atoms to which they are attached are pyrrolidine; A^3 and A^4 , together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} ; and one of R^{1A} and R^{1B} is H, and the other is R^1 , $C(O)R^1$, $C(O)NHR^1$, or $C(O)N(R^1)_2$ as in Formula

25 (XI); and R^1 is R^2 , R^3 , R^4 or R^5 ; R^2 is phenyl; R^3 is heteroarene; R^4 is cycloalkyl or heterocycloalkyl; R^5 is alkyl which is unsubstituted or substituted with one or two of independently selected R^6 , NHR^6 , $N(R^6)_2$, $C(O)R^6$, $NR^6C(O)R^6$, or $NR^6S(O)_2R^6$; R^6 is R^7 ,

R^8 , R^9 or R^{10} ; R^7 is phenyl; R^8 is heteroarene; R^9 is cycloalkyl or heterocycloalkyl; R^{10} is alkyl which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, $N(R^{11})_2$, $C(O)R^{11}$, or $C(O)OR^{11}$; R^{11} is R^{12} , R^{14} or R^{14A} ; R^{12} is phenyl; R^{14} is cycloalkyl or heterocycloalkyl; R^{14A} is alkyl; wherein the moieties represented by R^2 , R^4 , and R^9 are independently unsubstituted independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$, or (O); wherein R^{15} is R^{18} or R^{19} ; R^{18} is heterocycloalkyl; R^{19} is alkyl; wherein the moieties represented by R^{18} are independently unsubstituted or independently substituted with R^{23} ; wherein R^{23} is R^{27} ; R^{27} is alkyl each of which is substituted with R^{28} ; and R^{28} is phenyl.

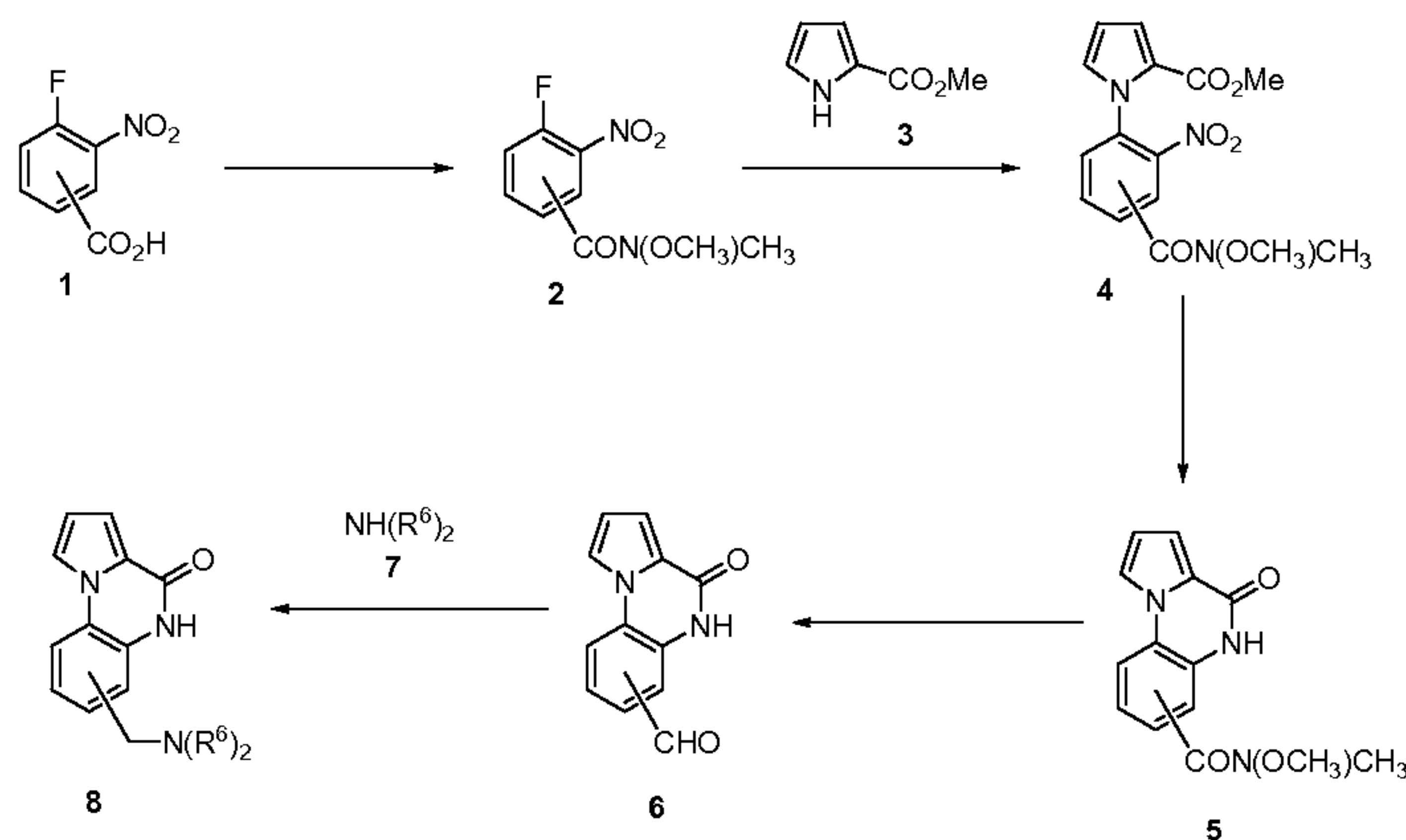
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Schemes

The starting materials used herein are commercially available or may be prepared by routine methods well known to those of ordinary skill in the art. The compounds of the present invention may be prepared using the methods illustrated in the general synthetic schemes and experimental procedures detailed below. The general synthetic schemes are presented for purposes of illustration and are not intended to be limiting.

15

Scheme 1



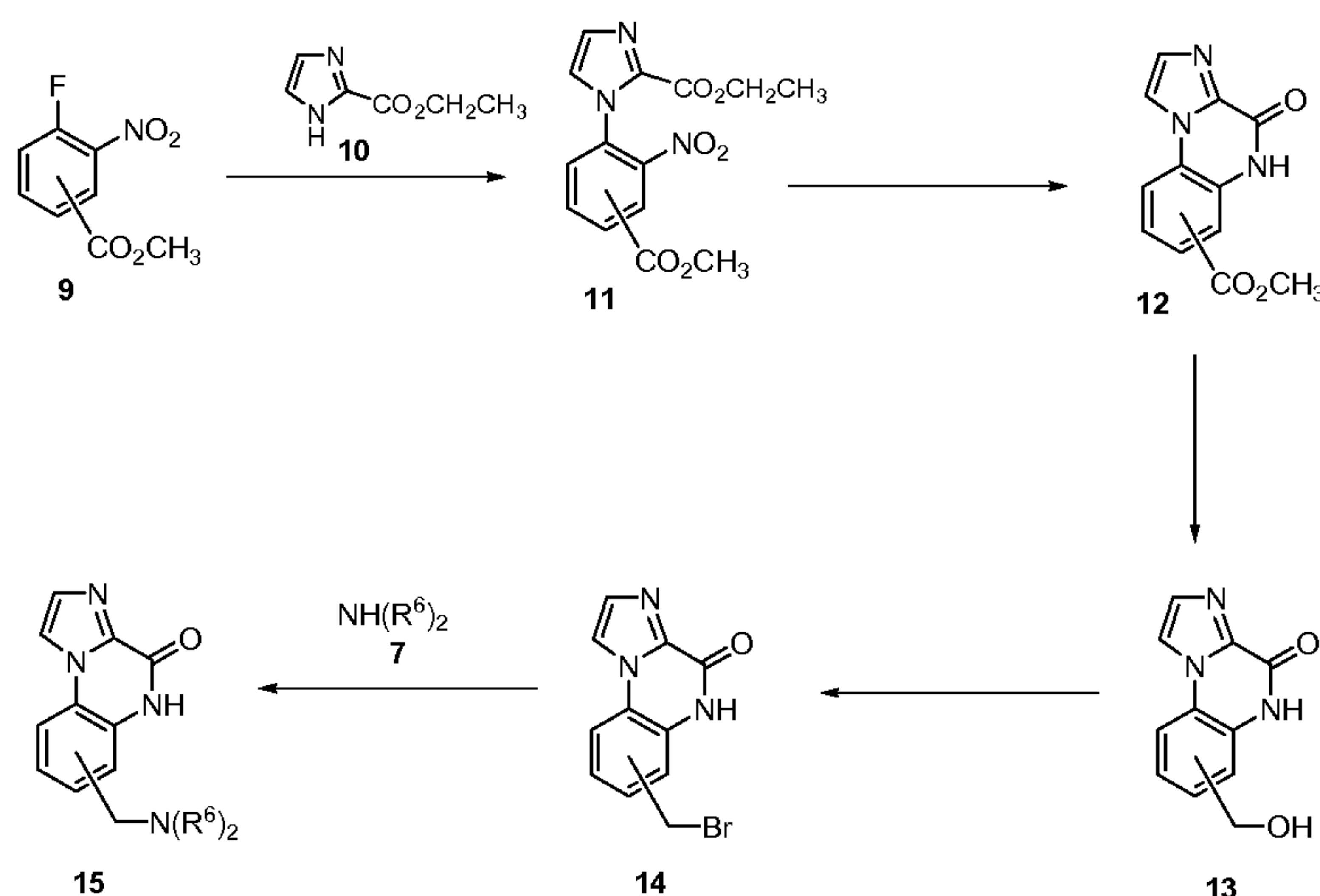
As shown in Scheme 1, a fluoro-nitrobenzoic acid of Formula (1) can be converted to a Weinreb amide of Formula (2) using amide bond formation conditions known to those skilled in the art and widely available in the literature. Reaction of a compound of Formula (2) with methyl 1H-pyrrole-2-carboxylate (3) using a base such as but not limited to cesium carbonate will provide a compound of Formula (4). The reaction is typically performed at room temperature or elevated temperatures in a solvent such as but not limited to DMF, THF, and the like. Compounds of Formula (4) can be converted to compounds of Formula (5) by reducing the nitro group of (4) to the amine under palladium

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catalyzed hydrogenation conditions, followed by heating. Typical hydrogenation conditions include the use of a catalyst such as but not limited to palladium on carbon, along with hydrogen gas in a solvent such as but not limited to methanol. Reduction of the Weinreb amide of Formula (5) will provide the corresponding aldehyde of Formula (6).

- 5 The reaction is typically performed below room temperature using a reducing agent such as but limited to lithium aluminum hydride in a solvent such as but not limited to DMF, THF, and the like. Compounds of Formula (8) can be prepared by reacting compounds of Formula (6) with amines of Formula (7) wherein each R_6 is H or is as described in Formula (I) or wherein $NH(R_6)_2$ is a heterocyclic amine of Formula R^9 . Typical reaction
- 10 conditions include the addition of a reducing agent such as but not limited to sodium triacetoxyborohydride, and acetic acid. The reaction can be performed at or above room temperature in a solvent such as dichloromethane, dichloroethane and the like.

Scheme 2

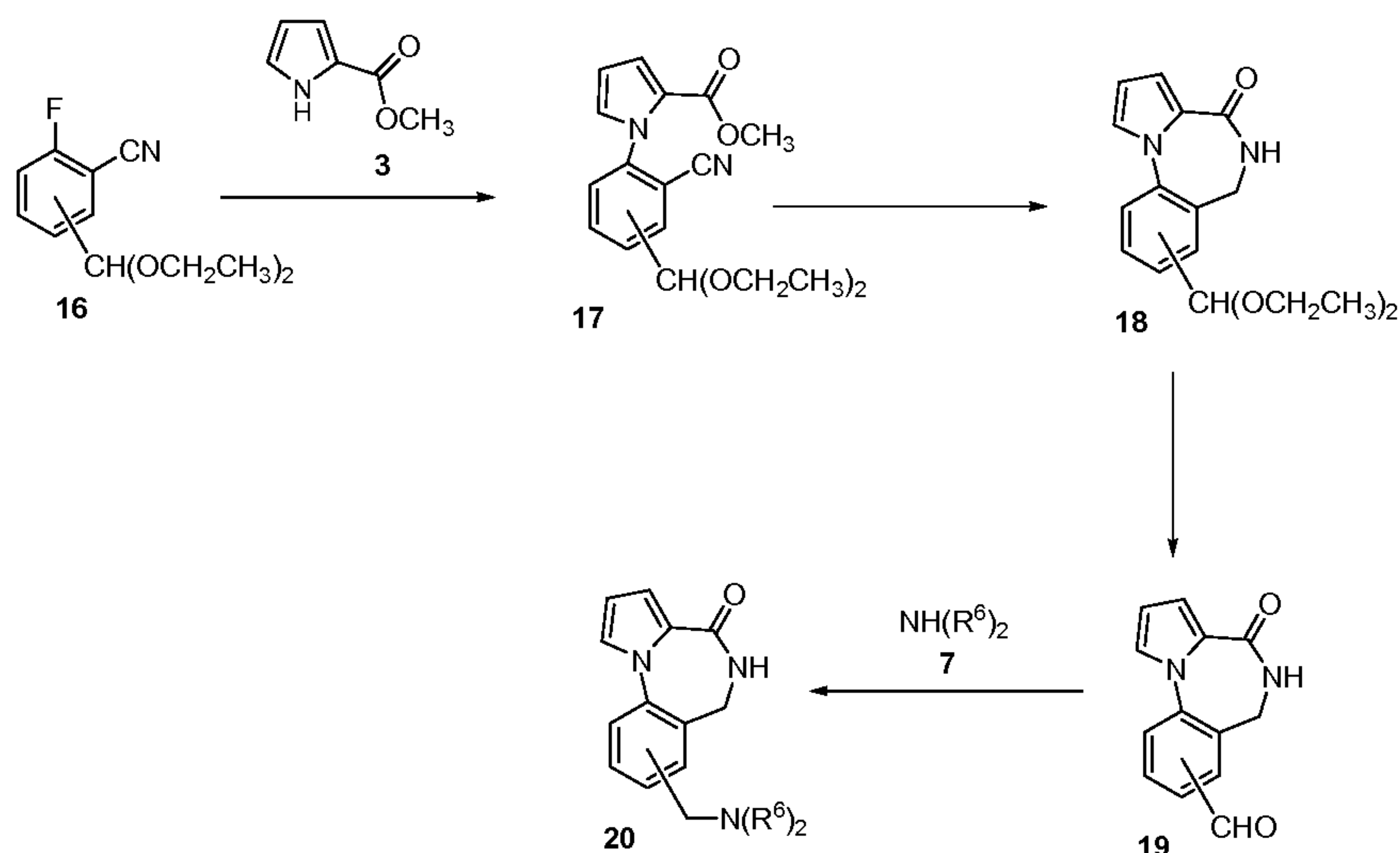


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- Reaction of a fluoro-nitrobenzoate of Formula (9), which can be prepared as described in Example 21A, with ethyl imidazole-2-carboxylate (10) and a base such as but not limited to cesium carbonate, will provide compounds of Formula (11). The reaction is
- 20 typically performed at room temperature or elevated temperatures in a solvent such as but not limited to DMF, THF, and the like. Compounds of Formula (11) can be converted to compounds of Formula (12) by reducing the nitro group of (11) to the corresponding amine under palladium catalyzed hydrogenation conditions, followed by heating. Typical hydrogenation conditions include the use of a catalyst such as but not limited to palladium

on carbon, along with hydrogen gas in a solvent such as but not limited to methanol. Reduction of the ester of Formula (12) to the corresponding alcohol of Formula (13) can be accomplished using a reducing agent such as but limited to lithium aluminum hydride. The reaction is typically performed below room temperature in a solvent such as but not limited to DMF, THF, and the like. Alcohols of Formula (13) can be converted to bromides of Formula (14) by treatment with phosphorus tribromide at room temperature in a solvent such as but not limited to dioxane. Reaction of (14) with a primary or secondary amine of Formula (7) (wherein each R_6 is H or is as described in Formula (I)) at room temperature will provide the benzylic amine of Formula (15). Additionally, a heterocyclic amine (R_9) may be used in place of $N(R_6)_2$. The reaction is typically performed in a solvent such as but not limited to acetonitrile.

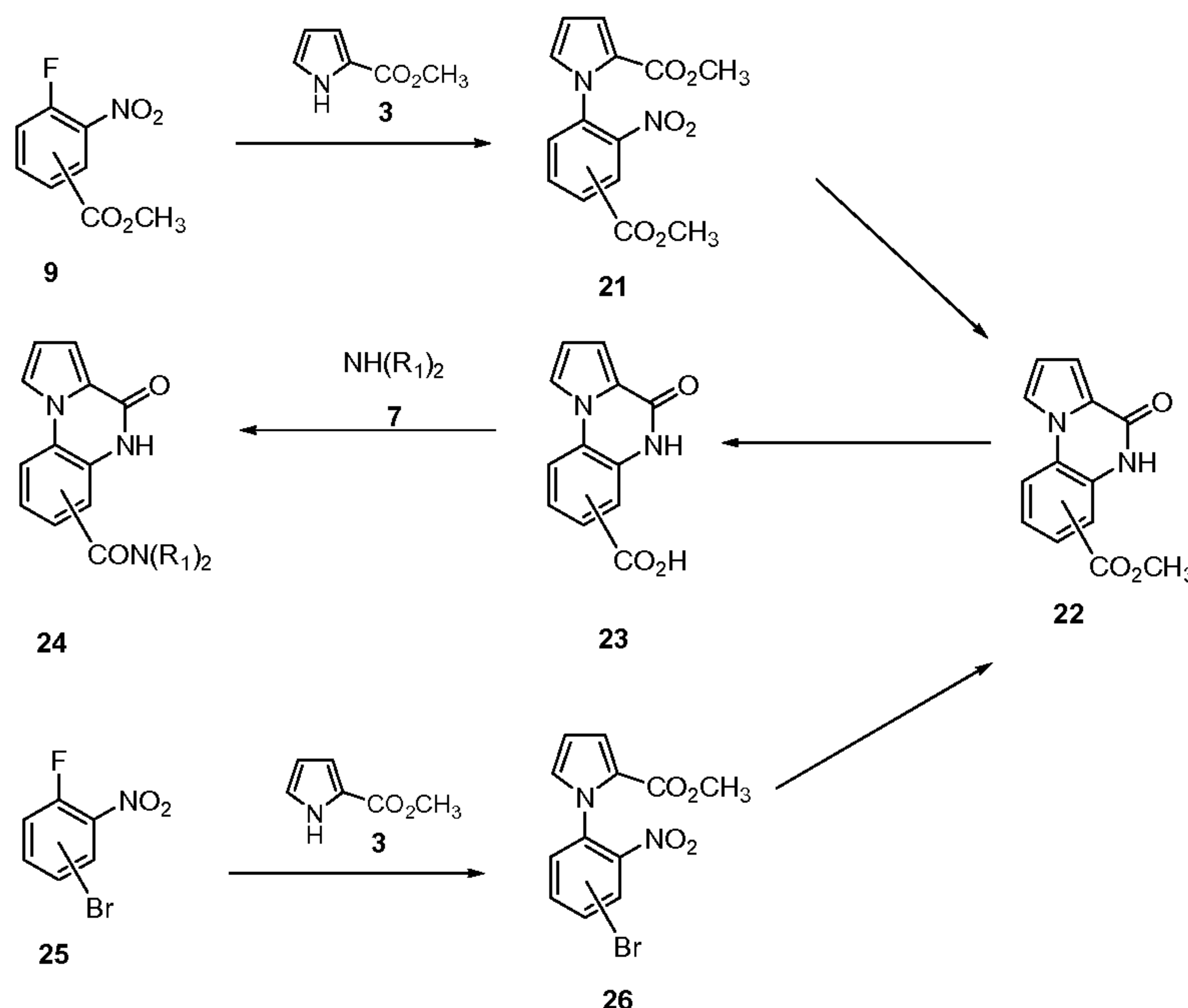
Scheme 3



As shown in Scheme 3, a fluoro-cyanobenzaldehyde acetal of Formula (16), which can be prepared as described in Example 26A, can be reacted with methyl-1H-pyrrole-2-carboxylate (3) to provide the coupled compound of Formula (17). The reaction typically requires a base such as but not limited to cesium carbonate, and is performed at room temperature or elevated temperatures in a solvent such as but not limited to DMF, THF, and the like. Reduction of the cyano group on the compound of Formula (17) to the benzylic amine under standard Raney nickel reduction conditions, will also result in ring closure and provide the lactam of Formula (18). Treatment of a compound of Formula (18) with an acid such as but not limited to hydrochloric acid, will provide an aldehyde of Formula (19). The reaction is typically performed at room temperature in an aqueous solvent such as but not limited to THF, dioxane, and the like. Compounds of Formula (20)

can be prepared by reacting compounds of Formula (19) with amines of Formula (7) wherein each R_6 is H or is as described in Formula (I) or wherein $N(R_6)_2$ is a heterocyclic amine of Formula R^9 . Typical reaction conditions include addition of a reducing agent such as but not limited to sodium triacetoxyborohydride, and acetic acid. The reaction can be performed at or above room temperature in a solvent such as dichloromethane, dichloroethane and the like.

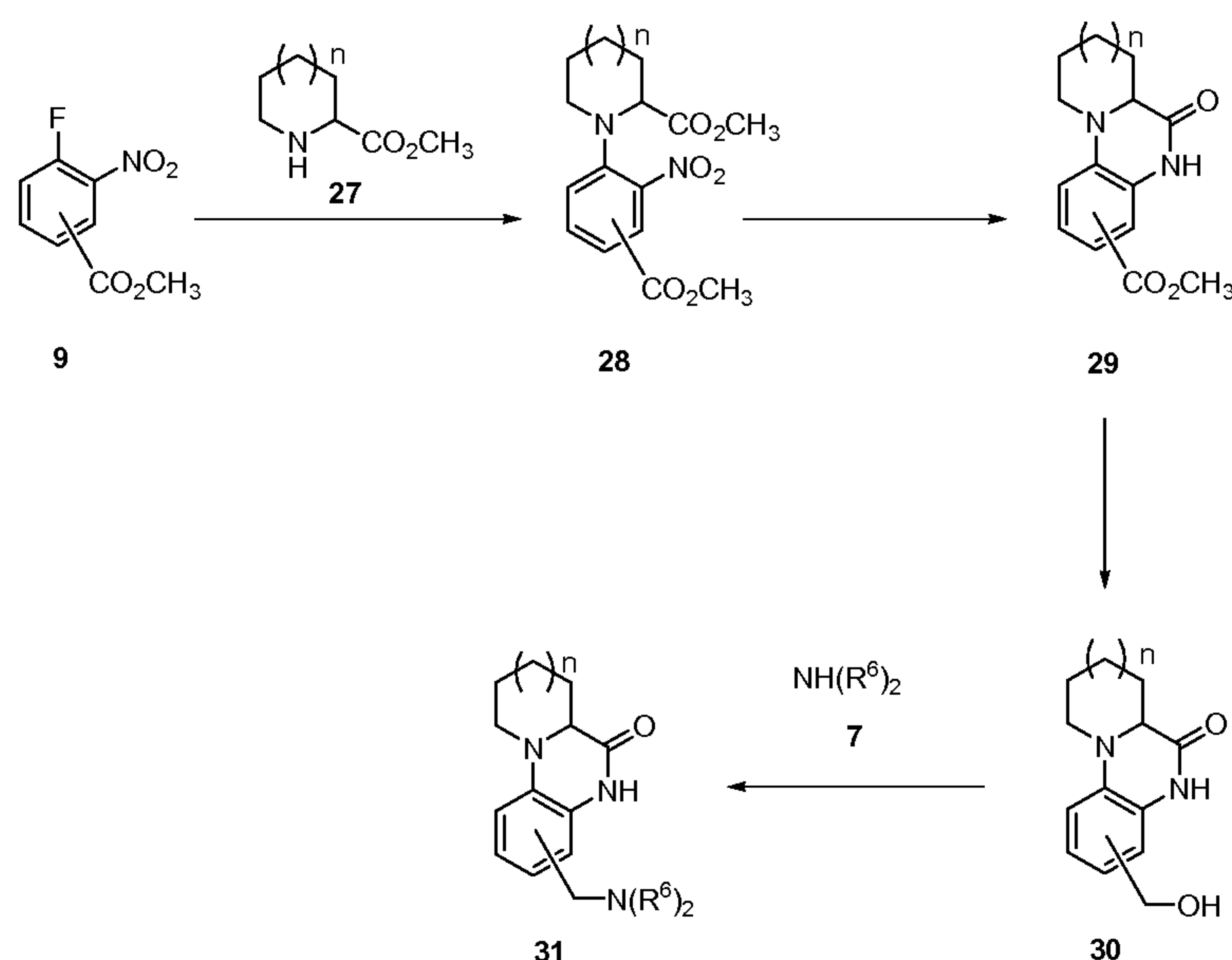
Scheme 4



A fluoro-nitrobenzoate of Formula (9) can be reacted with methyl 1H-pyrrole-2-carboxylate (3) and a base such as but not limited to cesium carbonate to provide the coupled compound of Formula (21). The reaction is typically performed at elevated temperatures in a solvent such as but not limited to THF, DMF and the like. Reduction of the nitro group on the compound of Formula (21) to the benzylic amine under standard Raney nickel reduction conditions, will also result in ring closure and provide the lactam of Formula (22). Saponification of the ester of Formula (22) with aqueous lithium hydroxide will provide the acid of Formula (23). The reaction may be performed in a solvent such as THF, methanol, or combinations thereof. Coupling an acid of Formula (23) with a primary or secondary amine of Formula (7) (wherein R_1 is H or is as described in Formula (I) or wherein $N(R_1)_2$ is a heterocyclic amine of Formula R^4), under standard peptide bond forming conditions known to those skilled in the art and widely available in the literature, will provide an amide of Formula (24). Alternatively, a fluoro-nitro-

bromobenzene of Formula (25) can be reacted with methyl 1H-pyrrole-2-carboxylate (3) and a base such as but not limited to cesium carbonate to provide the coupled compound of Formula (26). Compounds of Formula (26) can be converted to compounds of Formula (22) using palladium-catalyzed carbonylation conditions in the presence of methanol, which will result in both reduction of the nitro group and ring closure to give the lactam of Formula (22). The reaction is typically performed at elevated temperatures. In addition to methanol and carbon monoxide, a base such as but not limited to triethylamine and a catalyst such as but not limited to dichloro[1,1'-ferrocenylbis(diphenylphosphine)]palladium(II) dichloromethane are typically employed.

10

Scheme 5

A fluoro-nitrobenzoate of Formula (9) can be reacted with a cyclic amine of Formula (27), wherein n is 0 or 1, and a base such as but not limited to cesium carbonate to provide a coupled compound of Formula (28). The reaction is typically performed at elevated temperatures in a solvent such as but not limited to DMF. Compounds of Formula (28) can be converted to compounds of Formula (29) by reducing the nitro group of (28) to the amine under palladium catalyzed hydrogenation conditions, followed by heating. Typical hydrogenation conditions include the use of a catalyst such as but not limited to palladium on carbon, along with hydrogen gas in a solvent such as but not limited to methanol. Reduction of the ester of Formula (29) to the corresponding alcohol of Formula (30) can be accomplished using a reducing agent such as but not limited to lithium

aluminum hydride in a solvent such as but not limited to THF. The reaction is typically conducted below room temperature before quenching with hydrochloric acid. Compounds of Formula (30) can be converted to compounds of Formula (31) using standard Mitsunobu reaction conditions known to those skilled in the art and widely available in the literature, wherein R_6 is H or is as described in Formula (I) or wherein $N(R_6)_2$ is a heterocyclic amine of Formula R^9 .

The following examples are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention. The exemplified compounds were named using ACD/ChemSketch Version 5.06 (05 June 2001, Advanced Chemistry Development Inc., Toronto, Ontario). Intermediates were named using IUPAC standards.

EXAMPLE 1

7-((cyclohexylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

EXAMPLE 1A

To a solution of 4-fluoro-3-nitrobenzoic acid (1.54 g) in 30 mL methylene chloride was added 3 mL oxalyl chloride (34.4 mmol) followed by 0.1 mL DMF. The reaction was stirred overnight at room temperature. After concentrating, the concentrate was dissolved in 50 mL methylene chloride and 5 mL N,N'-diisopropylethylamine was added slowly followed by N,O-dimethylhydroxylamine hydrochloride (1.08 g). After 8 hours at room temperature, the crude reaction was filtered through silica gel (10 g) eluting with 1:1 ethyl acetate:hexane. This example was used in the next step without any further purification. ^1H NMR (300 MHz, DMSO- d_6) δ 8.36 (dd, 1H), 8.06 (m, 1H), 7.69 (m, 1H), 3.58 (s, 3H), 3.31 (s, 3H).

EXAMPLE 1B

Methyl 1H-pyrrole-2-carboxylate (3.2 g), EXAMPLE 1A (5.38 g) and cesium carbonate (11.73 g) were stirred in 20 mL DMF at room temperature for 48 hours. The reaction mixture was partitioned between ethyl acetate and H_2O . The aqueous phase was extracted with 6 x 40 mL ethyl acetate. The extract were dried over MgSO_4 , filtered and concentrated. The crude product was purified on silica gel (120 g) eluting with 1:1 ethyl

acetate:hexane. ¹H NMR (300 MHz, DMSO-d₆)

δ 8.35 (δ, 1H), 8.03 (δδ, 1H), 7.67 (δ, 1H), 7.35(t, 1H), 7.08 (m, 1H), 6.42 (m, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 3.34 (s, 3H).

5

EXAMPLE 1C

The product from EXAMPLE 1B (2.81 g) was dissolved in 30 mL methanol. While stirring vigorously, 10% Pd/C (286 mg) was added and the reaction was stirred under a H₂ balloon for 24 hours. The catalyst was removed by filtering through Celite. After concentrating the filtrate, the oil was dissolved in 40 mL dioxane and refluxed for 3 hours.

10

The crude product was purified on silica gel (90 g) eluting with 5/95 2M ammonia in methanol/methylene chloride to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 11.38 (βρ σ, 1H), 8.23 (μ, 1H), 8.10 (d, 1H), 7.60 (s, 1H), 7.48 (d, 1H), 7.07 (m, 1H), 6.73 (m, 1H), 3.59 (s, 3H), 3.29 (s, 3H).

15

EXAMPLE 1D

The product from EXAMPLE 1C (1.4 g) was dissolved in 40 mL THF and cooled to 0° under N₂. To the cooled solution was added 1M lithium aluminum in THF (10 mL) over 5 minutes. After 0.5 hours, the reaction was quenched 1M HCl. The solid was filtered and purified on silica gel (40 g) eluting with 1:1 ethyl acetate:hexane to provide This example.

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¹H NMR (300 MHz, DMSO-d₆) δ 11.52(s, 1H), 9.99 (s, 1H), 8.27 (m, 2H), 7.78 (m, 2H), 7.11 (m, 1H) 6.77 (m, 2H),

EXAMPLE 1E

7-((cyclohexylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

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EXAMPLE 1D (63 mg), cyclohexylamine (157 mg), sodium triacetoxyborohydride (83 mg) and 6 drops acetic acid were combined in 5 mL dichloroethane. After stirring at room temperature overnight, the mixture was concentrated and the concentrate was purified on silica gel (12 g) eluting with 1:1 ethyl acetate to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 11.26 (br s, 1H), 8.16 (s, 1H), 8.00 (d, 1H), 7.32 (s, 1H), 7.23 (d, 1H), 7.02 (m, 1H), 6.88 (t, 1H), 3.87 (br s, 2H), 1.91 (m, 2H), 1.69 (m, 2H), 1.55 (m, 1H), 1.19 (m, 6H).

30

EXAMPLE 2

7-(((cyclohexylmethyl)amino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 1E, substituting aminomethylcyclohexane (76 mg) for cyclohexylamine. This example was isolated after purification by RP-HPLC using a gradient elution of 10/90 acetonitrile/0.1% TFA in water to 50/50 at 254 nm over 30 minutes. ¹H NMR (300 MHz, DMSO-d₆) δ 11.49 (s, 1H), 8.21 (m, 1H), 8.12 (d, 1H), 7.38 (m, 2H), 7.05 (m, 1H), 6.72 (m, 1H), 4.17 (br t, 2H), 2.80 (m, 2H), 1.69 (m, 6H), 1.19 (m, 3H), 0.95 (m, 2H).

EXAMPLE 3

10 7-((cyclobutylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 2, substituting cyclobutylamine for aminomethylcyclohexane. ¹H NMR (300 MHz, DMSO-d₆) δ 11.49 (s, 1H), 8.21 (m, 1H), 8.12 (d, 1H), 7.30 (m, 2H), 7.06 (m, 1H), 6.72 (m, 1H), 4.07 (br s, 2H), 3.75 (m, 1H), 2.18 (m, 4H), 1.79 (m, 2H).

15

EXAMPLE 4

7-((cyclopentylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 2, substituting cyclopentylamine for aminomethylcyclohexane. ¹H NMR (300 MHz, DMSO-d₆) δ 11.49 (s, 1H), 8.21 (s, 1H), 8.13 (d, 1H), 7.34 (m, 2H), 7.06 (d, 1H), 6.72 (m, 1H), 4.18 (br s, 2H), 3.52 (br t, 1H), 2.00 (m, 2H), 1.63 (m, 6H).

20

EXAMPLE 5

7-((cyclopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 2, substituting cyclopropylamine for aminomethylcyclohexane. ¹H NMR (300 MHz, DMSO-d₆) δ 11.49 (s, 1H), 8.21 (s, 1H), 8.13 (d, 1H), 7.35 (m, 2H), 7.05 (m, 1H), 6.72 (t, 1H), 2.72 (m, 1H), 0.81 (m, 4H).

25

EXAMPLE 6

30 7-(piperidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 1E, substituting piperidine for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.17 (s, 1H), 8.14 (m, 1H), 7.95 (d, 1H), 7.25 (s, 1H), 7.10 (br d, 1H), 7.00 (dd, 1H), 6.79 (m, 1H), 3.44 (s, 2H), 2.33 (m,

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4H), 1.49 (m, 6H).

EXAMPLE 7

7-(pyrrolidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

5 This example was prepared as described in EXAMPLE 1E, substituting pyrrolidine for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.17 (br s, 1H), 8.14 (m, 1H), 7.95 (d, 1H), 7.26 (br s, 1H), 7.11 (dd, 1H), 7.00 (m, 1H), 6.66 (m, 1H), 3.59 (s, 2H), 2.44 (m, 4H), 1.70 (4H).

10

EXAMPLE 8

8-((cyclohexylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

EXAMPLE 8A

15 To a solution of 3-fluoro-4-nitrobenzoic acid (1.09 g) in 30 mL methylene chloride was added 2 mL oxalyl chloride (23 mmol) followed by 0.1 mL DMF. The reaction was stirred overnight at room temperature. After concentrating, the concentrate was dissolved in 50 mL methylene chloride and 5 mL N,N'-diisopropylethylamine was added slowly followed by N,O-dimethylhydroxylamine hydrochloride (0.75 g). After 8 hours at room temperature, the crude reaction was filtered through silica gel (10 g) eluting with 1:1 ethyl acetate:hexane. The filtrate was concentrated to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 8.22 (t, 1H), 7.77 (dd, 1H), 7.62 (dt, 1H), 3.56 (s, 3H), 3.29 (s, 3H).

20

EXAMPLE 8B

25 Methyl 1H-pyrrole-2-carboxylate (0.716 g), EXAMPLE 8A (1.18 g) and cesium carbonate (3.28 g) were stirred in 20 mL DMF at room temperature for 48 hours. The reaction mixture was partitioned between ethyl acetate and H₂O. The aqueous phase was extracted with ethyl acetate. The extract were dried over MgSO₄, filtered and concentrated. The crude product was purified on silica gel (40 g) eluting with 1:1 ethyl acetate:hexane to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 8.21 (d, 1H), 7.90 (dd, 1H), 7.73 (d, 1H), 7.33 (d, 1H), 7.07 (m, 1H), 6.40 (m, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.29 (s, 3H).

30

EXAMPLE 8C

EXAMPLE 8B (0.434 g) was dissolved in 30 mL methanol. While the mixture

stirred vigorously, 10% Pd/C (40 mg) was added and the reaction was stirred under a H₂ balloon for 24 hours. The catalyst was removed by filtering through Celite. After concentrating, the resultant oil was dissolved in 40 mL dioxane and refluxed for 3 hours. The crude product was purified on silica gel (40 g) eluting with 5/95 2M ammonia in methanol/methylene chloride to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 11.43 (br s, 1H), 8.27 (m, 2H), 7.51 (dd, 1H), 7.31 (d, 1H), 7.05 (dd, 1H), 6.70 (q, 1H), 3.50 (s, 3H), 3.29 (s, 3H).

EXAMPLE 8D

EXAMPLE 8C (0.348 g) was dissolved in 20 mL THF and cooled to 0° under N₂. To the cooled solution was added 1M lithium aluminum in THF (2.5 mL) over 5 minutes. After 0.5 hours, the reaction was quenched 1M HCl. The solid was filtered and purified on silica gel (40 g) eluting with 1:1 ethyl acetate:hexane to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 11.68 (s, 1H), 9.98 (s, 1H), 8.60 (s, 1H), 8.34 (s, 1H), 7.83 (d, 1H), 7.44 (d, 1H), 7.09 (m, 1H), 6.74 (m, 1H),

EXAMPLE 8E

8-((cyclohexylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

EXAMPLE 8D (60 mg), cyclohexylamine (55 mg), sodium triacetoxyborohydride (71 mg) were combined with 6 drops acetic acid in 5 mL dichloroethane. After stirring at room temperature overnight, the reaction was concentrated and purified by RP-HPLC using a gradient elution of 10/90 acetonitrile/0.1% TFA in water to 50/50 at 254 nm over 30 minutes to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 11.40 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.40 (d, 1H), 7.32 (s, 1H), 7.07 (d, 1H), 6.75 (m, 1H), 4.20 (s, 2H), 3.04 (m, 1H), 2.11 (br d, 2H), 1.78 (br d, 2H), 1.61 (br d, 1H), 1.30 (m, 4H), 1.11 (m, 1H).

EXAMPLE 9

8-(((cyclohexylmethyl)amino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting aminomethylcyclohexane for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.40 (s, 1H), 8.15 (s, 1H), 8.02 (br s, 1H), 7.40 (d, 1H), 7.32 (d, 1H), 7.07 (m, 1H), 6.75 (t, 1H), 4.19 (s, 2H), 2.79 (br d, 2H), 1.70 (m, 6H), 1.19 (m, 3H), 0.93 (m, 2H).

EXAMPLE 10

7-((isopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 1E, substituting isopropylamine for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.16 (br s, 1H),
5 8.14 (m, 1H), 7.94 (d, 1H), 7.29 (br s, 1H), 7.18 (dd, 1H), 7.00 (dd, 1H), 6.66 (d, 1H), 3.71 (s, 2H), 2.72 (m, 1H), 1.02 (d, 6H).

EXAMPLE 11

7-((benzylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

10 This example was prepared as described in EXAMPLE 1E, substituting benzylamine for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.24 (br s, 1H), 8.15 (m, 1H), 7.99 (d, 1H), 7.28 (m 7H), 7.02 (m, 1H), 6.67 (m, 1H), 3.77 (br s, 4H).

EXAMPLE 12

15 8-((cyclopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting cyclopropylamine for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.38 (s, 1H),
8.17 (s, 1H), 8.03 (m, 1H), 7.40 (dd, 1H), 7.32 (d, 1H), 7.07 (m, 1H), 6.75 (m, 1H), 4.29 (s,
2H), 2.73 (m, 1H), 0.81 (m, 4H).

20

EXAMPLE 13

8-((isopropylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting isopropylamine for cyclohexylamine. This example was isolated after purification on silica
25 gel (12 g) eluting with 1:1 ethyl acetate:hexane. ¹H NMR (300 MHz, DMSO-d₆) δ 8.10 (m, 1H), 7.95 (s, 1H), 7.23 (m, 2H), 7.01 (m, 1H), 6.67 (t, 1H), 3.75 (s, 2H), 2.74 (m, 1H), 1.01 (d, 6).

EXAMPLE 14

30 This example was prepared as described in EXAMPLE 8E, substituting phenethylamine for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.39 (s, 1H), 8.17 (s, 1H), 8.03 (m, 1H), 7.30 (m, 7H), 7.08 (m, 1H), 6.75 (m, 1H), 4.26 (br s, 2H), 2.97 (t, 2H), 2.70 (t, 2H).

EXAMPLE 15

8-(pyrrolidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting pyrrolidine
5 for cyclohexylamine. This example was isolated after purification on silica gel (12 g) eluting with 1:1 ethyl acetate:hexane. ¹H NMR (300 MHz, DMSO-d₆) δ 11.19 (s, 1H), 8.18 (m, 1H), 7.93 (s, 1H), 7.24 (s, 1H), 7.02 (m, 2H), 6.67 (m, 1H), 3.62 (s, 2H), 2.45 (m, 4H), 1.70 (m, 4H).

10

EXAMPLE 16

8-((cyclobutylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting cyclobutylamine for cyclohexylamine. This example was isolated after purification on silica
gel (12 g) eluting with 1:1 ethyl acetate:hexane. ¹H NMR (300 MHz, DMSO-d₆) δ 11.21 (br
15 s, 1H), 8.14 (m, 1H), 7.97 (s, 1H), 7.25 (m, 2H), 7.02 (m, 1H), 6.69 (m, 1H), 3.60 (s, 2H), 3.20 (m, 1H), 2.08 (m, 2H), 1.73 (m, 2H), 1.59 (m, 2H).

EXAMPLE 17

8-(morpholin-4-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting morpholine
20 for cyclohexylamine. ¹H NMR (300 MHz, DMSO-d₆) δ 11.48 (s, 1H), 8.20 (s, 1H), 8.03 (m, 1H), 7.40 (q, 2H), 7.08 (m, 1H), 6.76 (m, 1H), 4.30 (s, 2H), 3.97 (m, 2H), 3.64 (m, 2H), 3.22 (m, 4H).

25

EXAMPLE 18

8-((cyclopentylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting cyclopentylamine for cyclohexylamine. This example was isolated after purification on
silica gel (12 g) eluting with 1:1 ethyl acetate:hexane. ¹H NMR (300 MHz, DMSO-d₆) δ
30 11.20 (br s, 1H), 8.14 (m, 1H), 7.98 (m, 1H), 7.25 (m, 2H), 7.02 (m, 1H), 6.68 (m, 1H), 3.72 (s, 2H), 2.99 (m, 1H), 1.66 (m, 4H), 1.39 (m, 4H).

EXAMPLE 19

8-(piperidin-1-ylmethyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting piperidine for cyclohexylamine. This example was isolated after purification on silica gel (12 g) eluting with 1:1 ethyl acetate:hexane. ¹H NMR (300 MHz, DMSO-d₆) δ 11.22 (s, 1H), 8.18 (m, 1H), 7.91 (s, 1H), 7.23 (q, 2H), 7.02 (m, 1H), 6.68 (m, 1H), 3.48 (s, 2H), 2.34 (m, 4H), 1.50 (m, 4H), 1.39 (m, 2H).

EXAMPLE 20

8-((benzylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 8E, substituting benzylamine for cyclohexylamine. This example was isolated after purification on silica gel (12 g) eluting with 1:1 ethyl acetate:hexane. ¹H NMR (300 MHz, DMSO-d₆) δ 11.38 (s, 1H), 8.28 (s, 1H), 8.05 (s, 1H), 7.53 (d, 1H), 7.42 (m, 4H), 7.31 (d, 2H), 7.06 (d, 1H), 6.74 (m, 1H), 4.19 (s, 2H), 4.15 (s, 2H).

EXAMPLE 21

7-(pyrrolidin-1-ylmethyl)imidazo[1,2-a]quinoxalin-4(5H)-one

EXAMPLE 21A

To 4-fluoro-3-nitrobenzoic acid (2.02 g) in 50 mL anhydrous methanol was added thionyl chloride (1.6 mL) slowly over 15 minutes, and the mixture was refluxed for 4 hours. Concentration provided This example. ¹H NMR (300 MHz, DMSO-d₆) δ 8.58 (dd, J=7.29, 2.20 Hz, 1 H) 8.34 (ddd, J=8.73, 4.32, 2.20 Hz, 1 H) 7.75 (dd, J=11.02, 8.65 Hz, 1 H) 3.91 (s, 3H).

EXAMPLE 21B

Ethyl imidazole-2-carboxylate (0.58 g, 4.1 mmol), EXAMPLE 21A (0.822 g) and cesium carbonate (1.78 g) were combined in 20 mL of DMF. The mixture was stirred at 55° C for 24 hours. The reaction was partitioned between ethyl acetate and water, and the aqueous phase was extracted with 4 x 40 mL of ethyl acetate. The extract were dried over MgSO₄, filtered and concentrated to provide This example which was used in the next step without any further purification. ¹H NMR (300 MHz, DMSO-d₆) δ 8.65 (d, J=2.03 Hz, 1 H) 8.39 (dd, J=8.31, 1.86 Hz, 1 H) 7.86 (d, J=8.14 Hz, 1 H) 7.75 (d, J=1.36 Hz, 1 H) 7.36 (s, 1 H) 4.11 (q, J=7.12 Hz, 2 H) 3.96 (s, 3 H) 1.10 (t, J=7.12 Hz, 3 H).

EXAMPLE 21C

EXAMPLE 21B (1.8 g) was dissolved in 30 mL methanol. While stirring vigorously, 10% Pd/C (130 mg) was added and the reaction was stirred under a H₂ balloon for 24 hours. The catalyst was removed by filtering through Celite. After concentrating the filtrate, the resultant oil was dissolved in 40 mL dioxane and refluxed for 5 hours. The crude product was obtained after concentration and was used in the next step without any further purification. ¹H NMR (300 MHz, DMSO-d₆) δ 12.00 (s, 1 H) 8.60 (d, J=1.36 Hz, 1 H) 8.24 (d, J=8.48 Hz, 1 H) 8.01 (d, J=1.70 Hz, 1 H) 7.84 (dd, J=8.65, 1.86 Hz, 1 H) 7.64 (d, J=1.36 Hz, 1 H) 3.90 (s, 3 H).

EXAMPLE 21D

EXAMPLE 21C (0.60 g) was dissolved in 30 mL THF and cooled to 0° C under N₂. To the cooled solution was added 1M lithium aluminum in THF (6 mL) over 5 minutes. After 0.5 hours at 0° C, the reaction was warmed to room temperature. After 1 hour at room temperature, the reaction was quenched with 2M HCl. The resultant solid was collected and washed with THF to provide This example. ¹H NMR (300 MHz, DMSO-d₆) δ 12.11 (s, 1 H) 8.65 (s, 1 H) 8.12 (d, J=8.42 Hz, 1 H) 7.78 (s, 1 H) 7.43 (s, 1 H) 7.26 (d, J=8.42 Hz, 1 H) 4.59 (s, 2 H).

EXAMPLE 21E

EXAMPLE 21D (0.284 g) was dissolved in 10 mL of dioxane and phosphorous tribromide (0.4 mL) was added. After stirring at room temperature for 24 hours, the resultant precipitate was collected, washed with water, and dried to provide This example. ¹H NMR (400 MHz, DMSO-d₆) δ 11.95 (s, 1 H) 8.54 (s, 1 H) 8.10 (d, J=8.59 Hz, 1 H) 7.61 (s, 1 H) 7.44 (s, 1 H) 7.38 (d, J=8.59 Hz, 1 H) 4.80 (s, 3 H).

EXAMPLE 21F

7-(pyrrolidin-1-ylmethyl)imidazo[1,2-a]quinoxalin-4(5H)-one

EXAMPLE 21E (60 mg) and pyrrolidine (110 mg) were stirred in 2 mL of acetonitrile at 60° for 24 hours. The solid was collected by filtration and washed with ethyl acetate to provide This example. ¹H NMR (500 MHz, DMSO-d₆) δ 11.77 (s, 1 H) 8.51 (d, J=1.22 Hz, 1 H) 8.04 (d, J=8.24 Hz, 1 H) 7.59 (d, J=1.22 Hz, 1 H) 7.36 (d, J=1.22

Hz, 1 H), 7.22 (dd, J=8.39, 1.68 Hz, 1 H) 3.63 (s, 2 H) 2.45 (s, 4 H) 1.71 (m, 4H).

EXAMPLE 22

7-(piperidin-1-ylmethyl)imidazo[1,2-a]quinoxalin-4(5H)-one

5 This example was prepared as described in EXAMPLE 21F substituting piperidine (194 mg) for pyrrolidine. ¹H NMR (500 MHz, DMSO-d₆) δ 11.79 (s, 1 H) 8.51 (s, 1 H) 8.05 (d, J=7.93 Hz, 1 H) 7.59 (s, 1 H) 7.36 (s, 1 H) 7.22 (s, 1 H) 3.48 (br s, 2 H) 2.36 (m, 4H) 1.52 (s, 4 H), 1.41 (s, 2H).

10

EXAMPLE 23

7-((dimethylamino)methyl)imidazo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 21F substituting 2.0 M dimethylamine in THF (4 mL) for pyrrolidine. ¹H NMR (400 MHz, DMSO-d₆) δ 11.91 (s, 1 H) 8.55 (s, 1 H) 8.11 (d, J=8.29 Hz, 1 H) 7.60 (s, 1 H) 7.37 (s, 1 H) 7.27 (d, J=7.98 Hz, 1 H) 3.70 (br s, 2 H) 2.33 (br s, 6 H).

15

EXAMPLE 24

7-(((cyclohexylmethyl)amino)methyl)imidazo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 21F substituting aminomethylcyclohexane (213 mg) for pyrrolidine. ¹H NMR (500 MHz, DMSO-d₆) δ 11.90 (br s, 1H), 8.52 (s, 1 H) 8.06 (d, J=8.24 Hz, 1 H) 7.59 (s, 1 H) 7.39 (s, 1 H) 7.29 (d, J=7.93 Hz, 1 H) 3.83 (s, 2 H) 2.42 (m, 2 H) 1.68 (m, 5 H) 1.46 (m, 1 H) 1.18 (m, 3 H), 0.88 (m, 2 H).

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EXAMPLE 25

7-(morpholin-4-ylmethyl)imidazo[1,2-a]quinoxalin-4(5H)-one

This example was prepared as described in EXAMPLE 21F substituting morpholine (244 mg) for pyrrolidine. ¹H NMR (500 MHz, DMSO-d₆) δ 11.82 (s, 1 H) 8.52 (s, 1 H) 8.06 (d, J=8.24 Hz, 1 H) 7.59 (s, 1 H) 7.37 (s, 1 H) 7.24 (d, J=7.93 Hz, 1 H) 3.58 (m, 6 H), 2.42 (m, 4 H).

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EXAMPLE 26

8-((dimethylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

EXAMPLE 26A

2-Fluoro-5-formylbenzonitrile (1.62 g), triethyl orthoformate (2 mL) and ammonium nitrate (160 mg) were refluxed in 40 mL of ethanol for 24 hours. The reaction
5 was concentrated and partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over MgSO_4 , filtered, and concentrated. The concentrate was purified on silica gel (40 g) eluting with 1:4 ethyl acetate:hexane to provide This example. ^1H NMR (300 MHz, DMSO-d_6) δ 7.88 (dd, $J=6.27, 2.20$ Hz, 1 H) 7.76 (m, 1 H) 7.54 (t, $J=8.99$ Hz, 1 H) 5.54 (s, 1 H) 3.53 (m, 4 H) 1.16 (t, $J=6.95$ Hz, 6 H).

10

EXAMPLE 26B

Methyl 1H-pyrrole-2-carboxylate (263 mg), EXAMPLE 26A (0.470 mg) and cesium carbonate (862 mg) stirred in 8 mL DMF at 55° overnight. The reaction was concentrated and purified on silica gel (40 g) eluting with 1:4 ethyl acetate to provide This
15 example. ^1H NMR (500 MHz, DMSO-d_6) δ 7.90 (d, $J=1.83$ Hz, 1 H) 7.80 (dd, $J=8.24, 1.83$ Hz, 1 H) 7.58 (d, $J=8.24$ Hz, 1 H) 7.34 (m, 1 H) 7.11 (dd, $J=3.97, 1.83$ Hz, 1 H) 6.42 (dd, $J=3.97, 2.75$ Hz, 1 H) 5.63 (s, 1 H) 3.64 (s, 3H), 3.58 (m, 4 H) 1.19, (t, $J=7.02$ Hz, 6 H).

20

EXAMPLE 26C

EXAMPLE 26B (343 mg) was dissolved in 7M ammonia in methanol (20 mL) and 50% Raney nickel in water (1.88 g) was added. The reaction was stirred vigorously for 5 hours and carefully filtered through Celite. This example was isolated after concentrating the filtrate.. ^1H NMR (300 MHz, DMSO-d_6) δ 8.30 (t, $J=5.26$ Hz, 1 H) 7.50 (m, 4 H)
25 6.88 (dd, $J=3.73, 1.70$ Hz, 1 H) 6.41 (m, 1 H) 5.54 (s, 1 H) 3.54 (m, 4 H) 1.17 (t, $J=7.12$ Hz, 6 H).

EXAMPLE 26D

EXAMPLE 26C (371 mg) was stirred in 6 mL 1:2 2M aqueous HCl:THF for 1
30 hour. After concentrating, the concentrate was washed with diethyl ether to provide This example. ^1H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 1 H) 8.42 (t, $J=5.43$ Hz, 1 H) 8.00 (m, 2 H) 7.74 (m, 1 H) 7.60 (m, 1 H) 6.95 (dd, $J=3.56, 1.86$ Hz, 1 H) 6.49 (m, 1 H) 4.20 (d, $J=5.43$ Hz, 2 H).

EXAMPLE 26E

8-((dimethylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

EXAMPLE 26D (57 mg), 2M dimethylamine in THF (1 mL), sodium
5 triacetoxyborohydride (86 mg) and 6 drops acetic acid were stirred in 5 mL
dichloroethane. After stirring at room temperature overnight, the reaction was
concentrated and purified on silica gel (12 g) eluting with 10/90 2M ammonia in
methanol/methylene chloride to isolate This example. ¹H NMR (500 MHz, DMSO-d₆) δ
8.31 (t, J=5.34 Hz, 1 H) 7.48 (m, 2 H) 7.36 (m, 2 H) 6.87 (dd, J=3.81, 1.68 Hz, 1 H) 6.40
10 (m, 1 H) 4.07 (d, J=5.19 Hz, 2 H) 3.44 (s, 2 H) 2.18 (s, 6 H).

EXAMPLE 27

8-(pyrrolidin-1-ylmethyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

This example was prepared as described in EXAMPLE 26E substituting
15 pyrrolidine (206 mg) for dimethylamine. ¹H NMR (400 MHz, DMSO-d₆) δ 8.33 (t,
J=5.37 Hz, 1 H) 7.46 (m, 4 H) 6.87 (dd, J=3.68, 1.84 Hz, 1 H) 6.40 (m, 1 H) 4.07 (d,
J=5.22 Hz, 2 H) 3.72 (br s, 2 H) 2.57 (m, 4 H) 1.74 (m, 4 H).

EXAMPLE 28

20 8-((isopropylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

This example was prepared as described in EXAMPLE 26E substituting
isopropylamine (133 mg) for dimethylamine. ¹H NMR (400 MHz, DMSO-d₆) δ 8.37 (t,
J=5.22 Hz, 1 H) 7.48 (m, 4 H) 6.87 (dd, J=3.68, 1.84 Hz, 1 H) 6.40 (m, 1 H) 4.06 (d,
J=4.60 Hz, 2 H) 3.81 (s, 2 H) 3.25 (d, J=6.44 Hz, 1 H) 2.82 (s, 1 H) 1.06 (d, J=6.45 Hz, 6
25 H).

EXAMPLE 29

8-((4-methylpiperazin-1-yl)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

30 This example was prepared as described in EXAMPLE 26E substituting N-methylpiperazine (82 mg) for dimethylamine. ¹H NMR (500 MHz, DMSO-d₆) δ 8.30 (t,
J=5.49 Hz, 1 H) 7.47 (m, 2 H) 7.37 (m, 2 H) 6.86 (dd, J=3.97, 1.83 Hz, 1 H) 6.40 (m, 1 H)
4.07 (d, J=5.19 Hz, 2 H) 3.48 (s, 2 H) 2.43 (m, 8 H) 2.17 (s, 3 H).

EXAMPLE 30

8-(((2-ethoxyethyl)(methyl)amino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

5 This example was prepared as described in EXAMPLE 26E substituting morpholine (174 mg) for dimethylamine. ¹H NMR (400 MHz, DMSO-d₆) δ 8.32 (t, J=5.37 Hz, 1 H) 7.48 (m, 2 H) 7.39 (m, 2 H) 6.87 (dd, J=3.84, 1.69 Hz, 1 H) 6.40 (m, 1 H) 4.07 (d, J=5.22 Hz, 2 H) 3.58 (br s, 4 H) 3.50 (br s, 2 H) 2.37 (br s, 4 H)

10 EXAMPLE 31

8-(((cyclohexylmethyl)amino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

This example was prepared as described in EXAMPLE 26E substituting aminomethylcyclohexane (96 mg) for dimethylamine. ¹H NMR (400 MHz, DMSO-d₆) δ 8.36 (t, J=5.37 Hz, 1 H) 7.49 (m, 4 H) 6.87 (dd, J=3.68, 1.84 Hz, 1 H) 6.41 (m, 1 H) 4.06 (d, J=4.60 Hz, 2 H) 3.85 (s, 2 H) 2.46 (d, J=6.75 Hz, 2 H) 1.76 (d, J=12.89 Hz, 2 H) 1.65 (m, 3 H) 1.49 (m, 1 H) 1.15 (m, 3 H) 0.89 (m, 2 H).

EXAMPLE 32

20 8-((benzylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

This example was prepared as described in EXAMPLE 26E substituting benzylamine (96 mg) for dimethylamine. ¹H NMR (400 MHz, DMSO-d₆) δ 8.33 (t, J=5.52 Hz, 1 H) 7.35 (m, 9 H), 6.87 (dd, J=3.68, 1.84 Hz, 1 H) 6.40 (m, 1 H) 4.07 (d, J=4.91 Hz, 2 H) 3.72 (s, 2 H) 3.70 (s, 2 H).

25

EXAMPLE 33

8-((cyclopentylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

This example was prepared as described in EXAMPLE 26E substituting cyclopentylamine (126 mg) for dimethylamine. ¹H NMR (500 MHz, DMSO-d₆) δ 8.37 (t, J=5.34 Hz, 1 H) 7.52 (m, 4 H) 6.88 (dd, J=3.66, 1.83 Hz, 1 H) 6.41 (m, 1 H) 4.07 (d, J=4.27 Hz, 2 H) 3.95 (s, 2 H) 3.25 (m, 1 H) 1.87 (m, 2 H), 1.69 (m, 2 H) 1.52 (m, 4 H).

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EXAMPLE 34

3-(pyrrolidin-1-ylmethyl)-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

EXAMPLE 34A

Ethyl pipercolinate (7.6 mL), EXAMPLE 61A (8.8 g), and cesium carbonate (15.8 g) were stirred in 20 mL N, N-dimethylformamide at 55° C for 24 hours. The reaction mixture was concentrated and purified on silica gel (120 g) eluting with 1:4 ethyl acetate:hexane to provide the title compound. MS (ESI) m/e 337 (M+H)⁺.

EXAMPLE 34B

EXAMPLE 34A (5.43 g) was dissolved in 50 mL ethyl acetate. While stirring vigorously, 10% Pd/C (411 mg) was added, and the mixture was stirred under a H₂ balloon for 12 hours. The catalyst was removed by filtering through Celite. After concentrating, the resultant oil was purified on silica gel (90 g) eluting with 1:1 ethyl acetate:hexane to provide the title compound. MS (ESI) m/e 260 (M+H)⁺.

EXAMPLE 34C

EXAMPLE 34B was dissolved in 25 mL anhydrous THF and cooled to 0° C under N₂. To the cooled solution was added 1 M lithium aluminum hydride in THF (11 mL) over 5 minutes. After 0.5 hours, the mixture was warmed to room temperature. The mixture was quenched after 1 hour at room temperature with 2 M HCl. The solid was filtered and collected to provide the title compound. MS (ESI) m/e 232 (M+H)⁺.

EXAMPLE 34D

3-(pyrrolidin-1-ylmethyl)-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one
EXAMPLE 34C (94 mg), methanesulfonyl chloride (0.04 mL) and triethylamine (0.08 mL) were stirred in 10 mL methylene chloride for 6 hours. After concentrating, the residue was dissolved in 5 mL methylene chloride and pyrrolidine (0.2 mL) was added. The mixture was stirred for 12 hours and concentrated. The title compound was obtained after purification on silica gel (12 g) eluting with 5/95 2M ammonia in methanol/methylene chloride. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 6.79 (m, 3H), 3.70 (br d, 1H), 3.40 (s, 2H), 3.38 (m, 1H), 2.62 (m, 1H), 2.37 (m, 4H), 2.02 (m, 1H), 1.83 (m, 1H), 1.67 (m, 5H), 1.44 (m, 3H).

EXAMPLE 35

3-[(dimethylamino)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

To a solution of EXAMPLE 34C (98 mg), 2M dimethylamine in THF (0.3 mL) and triphenylphosphine (165 mg) in 5 mL THF was added di-*tert*-butyl azodicarboxylate (145 mg). The mixture was stirred for 48 hours and was concentrated. The crude product was purified on silica gel (12 g) eluting with 2/98 2M ammonia in methanol/methylene chloride to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.32 (s, 1H), 6.77 (m, 3H), 3.71 (m, 1H), 3.38 (m, 1H), 3.22 (s, 2H), 2.62 (m, 1H), 2.10 (s, 6H), 2.04 (m, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.46 (m, 3H).

10

EXAMPLE 36

3-[(cyclohexylamino)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

The title compound was prepared as described in EXAMPLE 35, substituting cyclohexylamine for dimethylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 6.79 (m, 3H), 3.70 (d, 1H), 3.58 (s, 2H), 3.37 (m, 1H), 2.61 (m, 1H), 2.36 (m, 1H), 2.01 (m, 1H), 1.82 (m, 3H), 1.66 (m, 3H), 1.43 (m, 5H), 1.09 (m, 5H).

15

EXAMPLE 37

3-(piperidin-1-ylmethyl)-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

The title compound was prepared as described in EXAMPLE 35, substituting piperidine for dimethylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 6.75 (m, 3H), 3.70 (d, 1H), 3.39 (m, 1H), 3.26 (s, 2H), 2.62 (m, 1H), 2.27 (m, 4H), 2.02 (m, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.43 (m, 9H).

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EXAMPLE 38

3-[(isopropylamino)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

The title compound was prepared as described in EXAMPLE 35, substituting isopropylamine for dimethylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 6.75 (m, 3H), 3.74 (d, 1H), 3.54 (s, 2H), 3.37 (m, 1H), 2.69 (m, 1H), 2.61 (m, 1H), 2.02 (m, 1H), 1.82 (m, 1H), 1.67 (m, 1H), 1.44 (m, 4H), 0.98 (d, 6H).

30

EXAMPLE 39

3-{[ethyl(methyl)amino]methyl}-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

The title compound was prepared as described in EXAMPLE 35, substituting N-ethylmethylamine for dimethylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 6.77 (m, 3H), 3.70 (d, 1H), 3.39 (m, 1H), 3.29 (s, 2H), 2.62 (m, 1H), 2.33 (q, 2H), 2.06 (s, 3H), 2.03 (m, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.46 (m, 3H), 0.99 (t, 3H).

EXAMPLE 40

3-{[cyclohexyl(methyl)amino]methyl}-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

The title compound was prepared as described in EXAMPLE 35, substituting N-methylcyclohexylamine for dimethylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.28 (s, 1H), 6.78 (m, 3H) 3.70 (d, 1H), 3.39 (s, 2H) 3.36 (m, 1H), 2.61 (m, 1H), 2.36 (m, 1H), 2.06 (s, 3H), 2.01 (m, 1H), 1.75 (m, 6H), 1.48 (m, 4H), 1.16 (m, 5H).

15

EXAMPLE 41

3-{[isopropyl(methyl)amino]methyl}-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

The title compound was prepared as described in EXAMPLE 35, substituting N-methylisopropylamine for dimethylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.29 (s, 1H), 6.79 (m, 2H), 6.73 (d, 1H), 3.70 (d, 1H), 3.38 (m, 1H), 3.30 (s, 2H), 2.81 (m, 1H), 2.61 (m, 1H), 2.02 (m, 4H), 1.83 (m, 1H), 1.67 (m, 1H), 1.44 (m, 3H), 0.98 (d, 6H).

20

EXAMPLE 42

3-[(4-methylpiperazin-1-yl)methyl]-7,8,9,10-tetrahydro-5H-pyrido[1,2-a]quinoxalin-6(6aH)-one

The title compound was prepared as described in EXAMPLE 35, substituting N-methylpiperazine for dimethylamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.32 (s, 1H), 6.75 (m, 3H), 3.70 (d, 1H), 3.39 (m, 1H), 3.29 (s, 2H) 2.61 (m, 1H), 2.31 (m, 7H), 2.16 (s, 3H), 2.00 (m, 1H), 1.82 (m, 1H), 1.67 (m, 1H), 1.41 (m, 4H).

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EXAMPLE 43

7-(pyrrolidin-1-ylmethyl)-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

EXAMPLE 43A

Methyl pyrrolidine-2-carboxylate hydrochloride (3.13 g), EXAMPLE 61A (3.76 g), and cesium carbonate (12.2 g) were stirred in 15 mL N,N-dimethylformamide at 60° C for 12 hours. The reaction mixture was filtered through Celite and concentrated. The crude product was purified on silica gel (90 g) eluting with 1:4 ethyl acetate:hexane. MS (ESI) m/e 308 (M+H)⁺.

EXAMPLE 43B

EXAMPLE 43A (4.66 g) was dissolved in 50 mL methanol. While it was stirred vigorously, 10% Pd/C (460 mg) was added, and the mixture was stirred under a H₂ balloon for 12 hours. The catalyst was removed by filtering the mixture through Celite. After concentrating the filtrate, the crude product was used without any further purification. MS (ESI) m/e 246 (M+H)⁺.

EXAMPLE 43C

EXAMPLE 43B (122 mg) was dissolved in 10 mL anhydrous THF and cooled to 0° C. To the cooled solution was added 1M lithium aluminum hydride (1.2 mL). After stirring for 0.5 hours at 0° C, the mixture was warmed to room temperature and quenched after 1 hour with 2M HCl. The mixture was concentrated and purified on silica gel (4 g) eluting with 10/90 2M ammonia in methanol/methylene chloride. MS (ESI) m/e 219 (M+H)⁺.

EXAMPLE 43D

7-(pyrrolidin-1-ylmethyl)-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one
To a solution of EXAMPLE 43C (82 mg), pyrrolidine (131 mg) and triphenylphosphine (148 mg) in 5 mL THF was added di-*tert*-butyl azodicarboxylate (137 mg). The mixture was stirred for 48 hours and concentrated. The crude product was purified on silica gel (12 g) eluting with 10/90 2M ammonia in methanol/methylene chloride to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 6.79 (m, 2H), 6.50 (d, 1H), 3.51 (m, 1H), 3.42 (s, 2H), 3.38 (m, 1H), 3.02 (m, 1H), 2.39 (br s, 4H), 2.10 (m, 1H), 1.94 (m, 3H), 1.67 (br s, 4H).

EXAMPLE 44

7-[(dimethylamino)methyl]-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 43, substituting dimethylamine for pyrrolidine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 6.78 (m, 2H), 6.51 (d, 1H), 3.53 (m, 1H), 3.39 (m, 1H), 3.32 (s, 2H), 3.03 (m, 1H), 2.10 (s, 6H), 2.07 (m, 1H), 1.91 (m, 3H).

EXAMPLE 45

7-(piperidin-1-ylmethyl)-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 43, substituting piperidine for pyrrolidine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.25 (s, 1H), 6.77 (m, 2H), 6.51 (d, 1H), 3.52 (m, 1H), 3.39 (m, 1H), 3.26 (s, 2H), 3.03 (m, 1H), 2.27 (br s, 4H), 2.10 (m, 1H), 1.94 (m, 3H), 1.46 (m, 4H), 1.37 (m, 2H).

EXAMPLE 46

7-{[ethyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 43, substituting N-ethylmethylamine for pyrrolidine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 6.78 (m, 2H), 6.51 (d, 1H), 3.52 (m, 1H), 3.40 (m, 1H), 3.31 (s, 2H), 3.03 (m, 1H), 2.35 (m, 2H), 2.10 (m, 1H), 2.06 (s, 3H), 1.94 (m 3H), 1.00 (t, 3H).

EXAMPLE 47

7-{[cyclohexyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 43, substituting N-methylcyclohexylamine for pyrrolidine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.24 (s, 1H), 6.78 (m, 2H), 6.50 (d, 1H), 3.51 (m, 1H), 3.39 (m, 3H), 3.02 (m, 1H), 2.36 (m, 1H), 2.09 (m, 4H), 1.94 (m, 3H), 1.75 (m, 4H), 1.57 (m, 1H), 1.16 (m, 5H).

EXAMPLE 48

7-[(4-methylpiperazin-1-yl)methyl]-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 43, substituting N-methylpiperazine for pyrrolidine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 6.77 (m, 2H), 6.50 (d, 1H), 3.51 (m, 1H), 3.40 (m, 1H), 3.29 (s, 2H), 3.03 (m, 1H), 2.30 (m, 4H), 2.14 (s, 3H), 2.09 (m, 1H), 1.94 (m, 4H), 1.39 (m, 3H).

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EXAMPLE 49

7-{[benzyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 43, substituting N-methylbenzylamine for pyrrolidine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.30 (s, 1H), 7.32 (m, 4H), 7.23 (m, 1H), 6.87 (s, 1H), 6.83 (d, 1H), 6.53 (d, 1H), 3.53 (m, 1H), 3.44 (s, 2H), 3.41 (m, 1H), 3.36 (s, 2H), 3.05 (m, 1H), 2.10 (m, 1H), 2.04 (s, 3H), 1.93 (m, 3H).

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EXAMPLE 50

7-{[isopropyl(methyl)amino]methyl}-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoxalin-4(5H)-one

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The title compound was prepared as described in EXAMPLE 43, substituting N-methyisopropylamine for pyrrolidine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.24 (s, 1H), 6.80 (s, 1H), 6.78 (d, 1H), 6.51 (d, 1H), 3.50 (m, 1H), 3.39 (m, 1H), 3.30 (s, 2H), 3.01 (m, 1H), 2.80 (m, 1H), 2.09 (m, 1H), 2.01 (s, 3H) 1.94 (m, 3H), 0.97 (d, 6H).

20

EXAMPLE 51

N-cyclopropyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-8-yl)methyl]methanesulfonamide

To a solution of EXAMPLE 12 (26 mg) and triethylamine (25 μL) in 1 mL dioxane was added methanesulfonyl chloride (5.53 μL). The mixture was stirred for 24 hours and concentrated. The title compound was purified by RP-HPLC using a gradient elution of 10/90 to 70/30 acetonitrile/0.1% TFA in water at 254 nm over 30 minutes. The free base was isolated after eluting from an ion exchange column (10 g). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.28 (s, 1H), 8.14 (m, 1H), 7.95 (s, 1H), 7.29 (s, 2H), 7.03 (m, 1H), 6.70 (m, 1H), 4.41 (s, 2H), 2.96 (s, 3H), 2.46 (m, 1H), 0.68 (d, 4H).

30

EXAMPLE 52

7-[(2-oxopyrrolidin-1-yl)methyl]pyrrolo[1,2-a]quinoxalin-4(5H)-one

EXAMPLE 1D (45 mg), ethyl 4-aminobutanoate hydrochloride (49 mg), and triethylamine (0.04 mL) were dissolved in 5 mL anhydrous methanol. Sodium borohydride (8 mg) was added, and the mixture was stirred at 45° C for 12 hours. After concentrating *in vacuo*, the crude mixture was purified by RP-HPLC using a gradient elution of 10/90 to 50/50 acetonitrile/0.1 % TFA in water at 254 nm over 30 minutes. The title compound was obtained as the free base after eluting from an ion exchange column (5 g). ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.20 (br s, 1H), 8.16 (m, 1H), 8.01 (d, 1H), 7.15 (s, 1H), 7.07 (d, 1H), 7.02 (m, 1H), 6.68 (t, 1H), 4.40 (s, 2H), 3.26 (t, 2H), 2.31 (t, 2H), 1.95 (t, 2H).

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EXAMPLE 53

N-cyclobutyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-8-yl)methyl]ethanesulfonamide

The title compound was prepared as described in EXAMPLE 51, substituting EXAMPLE 16 for EXAMPLE 12 and substituting ethanesulfonyl chloride for methanesulfonyl chloride. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.25 (s, 1H), 8.06 (m, 1H), 7.95 (s, 1H), 7.28 (s, 2H), 7.03 (m, 1H), 6.70 (t, 1H), 4.54 (s, 2H), 4.25 (p, 1H), 3.09 (q, 2H), 2.13 (m, 2H), 2.02 (m, 2H), 1.15 (m, 2H), 1.21 (t, 3H).

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EXAMPLE 54

N-isopropyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-8-yl)methyl]benzenesulfonamide

The title compound was prepared as described in EXAMPLE 51, substituting EXAMPLE 13 for EXAMPLE 12 and substituting benzene sulfonyl chloride for methanesulfonyl chloride. The title compound was isolated after purification on silica gel (12 g) eluting with 2/98 ethanol/methylene chloride. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.26 s, 1H), 8.02 (m, 1H), 7.97 (s, 1H), 7.88 (s, 2H), 7.69 (d, 1H), 7.62 (t, 2H), 7.36 (d, 1H), 7.28 (d, 1H), 7.03 (d, 1H), 6.70 (d, 1H), 4.44 (s, 2H), 4.12 (sept, 1H), 0.89 (d, 6H).

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EXAMPLE 55

N-cyclobutyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]acetamide

The title compound was prepared as described in EXAMPLE 51, substituting EXAMPLE 3 for EXAMPLE 12 and substituting acetic anhydride for methanesulfonyl

chloride. The title compound was isolated after purification on silica gel (12 g) eluting with 5/95 2M ammonia in methanol/methylene chloride. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.86 (br s, 1H), 8.02 (m, 1H), 7.89 (d, 1H), 7.15 (s, 1H), 7.03 (s, 1H), 7.00 (m, 1H), 6.63 (m, 1H), 4.63 (s, 2H), 4.50 (m, 1H), 2.09 (m, 4H), 2.03 (s, 3H), 1.59 (m, 2H).

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EXAMPLE 56

N-cyclopropyl-N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]methanesulfonamide

The title compound was prepared as described in EXAMPLE 51, substituting
10 EXAMPLE 5 for EXAMPLE 12. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.24 (s, 1H), 8.16 (m, 1H), 8.02 (d, 1H), 7.32 (s, 1H), 7.17 (d, 1H), 7.03 (s, 1H), 6.68 (t, 1H), 4.39 (s, 2H), 2.96 (s, 3H), 2.47 (s, 1H), 0.68 (m, 4H).

EXAMPLE 57

15 8-(piperidin-1-ylmethyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

The title compound was prepared as described in EXAMPLE 26E, substituting piperidine for dimethylamine. The title compound was isolated as the TFA salt after purification by RP-HPLC using a gradient elution of 10/90 to 90/10 acetonitrile/0.1% TFA in water at 254 nm over 30 minutes. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.40 (t, 1H),
20 7.58 (m, 4H), 6.92 (m, 1H), 6.45 (m, 1H), 4.33 (d, 2H), 4.10 (d, 2H), 3.36 (br d, 2H), 2.90 (m, 2H), 1.83 (br d, 2H), 1.65 (m, 3H), 1.37 (m, 1H).

EXAMPLE 58

25 8-[(cyclohexylamino)methyl]-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one

The title compound was prepared as described in EXAMPLE 26E, substituting cyclohexylamine for dimethylamine. The title compound was isolated as the TFA salt after purification by RP-HPLC using a gradient elution of 10/90 to 90/10 acetonitrile/0.1% TFA in water at 254 nm over 30 minutes. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.42 (t, 1H), 7.56 (m, 4H), 6.91 (m, 1H), 6.44 (m, 1H), 4.22 (t, 2H), 4.09 (br s, 2H),
30 3.04 (m, 1H), 2.10 (br d, 2H), 1.79 (br d, 2H), 1.63 (br d, 1H), 1.29 (m, 4H), 1.13 (m, 1H).

EXAMPLE 59

Methyl N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]glycinate

The title compound was prepared as described in EXAMPLE 1E, substituting glycine methyl ester hydrochloride for cyclohexylamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.46 (s, 1H), 9.51 (br s, 1H), 8.20 (m, 1H), 8.13 (d, 1H), 7.37 (s, 1H), 7.33 (d, 1H), 7.06 (d, 1H), 6.73 (q, 1H), 4.21 (s, 2H), 4.02 (s, 2H), 3.76 (s, 3H).

5

EXAMPLE 60

N-[(4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxalin-7-yl)methyl]glycine

EXAMPLE 59 (123 mg) was dissolved in 5 mL THF and 1 mL methanol to which 2 mL 1M lithium hydroxide was added. After stirring at room temperature for 12 hours, the solution was neutralized with 1M HCl. The solid was collected and dried to provide the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.99 (s, 1H), 7.93 (d, 1H), 7.40 (s, 1H), 7.30 (d, 1H), 7.06 (m, 1H), 6.64 (m, 1H), 4.20 (s, 2H), 3.81 (s, 2H).

10

EXAMPLE 61

4-oxo-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

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EXAMPLE 61A

A solution of 4-fluoro-3-nitrobenzoic acid (11.9 g) in 100 mL anhydrous methanol was cooled to 0° C. Thionyl chloride (9.5 mL) was added slowly over 10 minutes and the mixture was refluxed for 4 hours. The mixture was concentrated to provide the title compound. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.58 (dd, 1H), 8.35 (m, 1H), 7.75 (m, 1H), 3.01 (s, 3H).

20

25

EXAMPLE 61B

The title compound was prepared as described in EXAMPLE 34A, substituting methyl 1H-pyrrole-2-carboxylate for ethyl pipercolinate. MS (ESI) m/e 304(M+H)⁺.

EXAMPLE 61C

The title compound was prepared as described in EXAMPLE 43B, substituting EXAMPLE 61B for EXAMPLE 43A. The title compound was isolated after purification on silica gel (120 g) eluting with 4:1 ethyl acetate:hexanes. MS (ESI) m/e 242(M+H)⁺.

30

EXAMPLE 61D

EXAMPLE 61C (0.638 g) was dissolved in 25 mL 5:1 THF:methanol and 1M lithium hydroxide (13 mL) was added. The mixture was stirred for 12 hours then neutralized with 2 M HCl. The resultant solid was collected and recrystallized from hot
5 methanol. MS (ESI) m/e 229(M+H)⁺.

EXAMPLE 61E

4-oxo-N-(2-pyrrolidin-1-ylethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide
EXAMPLE 61D (70 mg), N,N-diisopropylethylamine (0.1 mL) and 2-(1H-7-
10 azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium
(HATU) (154 mg) were stirred in 1 mL N,N-dimethylformamide for 0.5 hours and 2-
(pyrrolidin-1-yl)ethanamine (82 mg) was added. After 24 hours, the mixture was
concentrated. The title compound was isolated after purification by RP-HPLC using a
gradient elution of 5/95 to 70/30 acetonitrile/0.1% TFA in water at 254 nm over 30
15 minutes. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.35 (br s, 1H), 8.49 (t, 1H), 8.23 (s, 1H),
8.12 (d, 1H), 7.79 (s, 1H), 7.68 (d, 1H), 7.07 (d, 1H), 6.73 (m, 1H), 3.39 (m, 2H), 2.61 (t,
2H), 2.52 (m, 4H), 1.69 (4H).

EXAMPLE 62

20 7-{[(2-pyrrolidin-1-ylethyl)amino]methyl}pyrrolo[1,2-a]quinoxalin-4(5H)-one
The title compound was prepared as described in EXAMPLE 1E, substituting 2-
(pyrrolidin-1-yl)ethanamine for cyclohexylamine. The title compound was purified by
RP-HPLC using a gradient elution of 5/95 to 70/30 acetonitrile/0.1% TFA in water at 254
nm over 30 minutes. The free base was isolated after eluting from an ion exchange
25 column (10 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.18 (br s, 1H), 8.14 (m, 1H), 7.97 (d,
1H), 7.27 (s, 1H), 7.16 (d, 1H), 7.01 (m, 1H), 6.66 (m, 1H), 3.74 (s, 2H), 2.61 (m, 2H),
2.53 (m, 2H), 2.43 (m, 4H), 1.66 (m, 4H).

EXAMPLE 63

30 N-(3-morpholin-4-ylpropyl)-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide
The title compound was prepared as described as in EXAMPLE 61E, substituting
3-morpholinopropan-1-amine for 2-(pyrrolidin-1-yl)ethanamine. The title compound was
isolated after purification on silica gel (12 g) eluting with 10/90 2M ammonia in

methanol/methylene chloride. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.36 (s, 1H), 8.57 (t, 1H), 8.24 (s, 1H), 8.13 (d, 1H), 7.78 (s, 1H), 7.68 (dd, 1H), 7.07 (m, 1H), 6.73 (m, 1H), 3.58 (m, 4H), 3.30 (m, 2H), 2.37 (m, 6H), 1.70 (t, 2H).

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EXAMPLE 64

N-(2-morpholino-2-oxoethyl)-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61, substituting 2-amino-1-morpholinoethanone hydrochloride for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.37 (s, 1H), 8.62 (t, 1H), 8.24 (s, 1H), 8.14 (d, 1H), 7.81 (s, 1H), 7.72 (dd, 1H), 7.07 (m, 1H), 6.73 (t, 1H), 4.16 (d, 2H), 3.61 (m, 4H), 3.48 (m, 4H).

10

EXAMPLE 65

7-([2-(dimethylamino)ethyl]amino)methylpyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 1E, substituting N¹, N¹-dimethylethane-1,2-diamine for cyclohexylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.25 (br s, 1H), 8.16 (s, 1H), 7.99 (d, 1H), 7.29 (s, 1H), 7.19 (d, 1H), 7.02 (m, 1H), 6.67 (t, 1H), 3.78 (s, 2H), 2.64 (t, 2H), 2.43 (t, 2H), 2.18 (s, 6H).

15

EXAMPLE 66

N-[3-(4-methylpiperazin-1-yl)propyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting 3-(4-methylpiperazin-1-yl)propan-1-amine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.37 (s, 1H), 8.57 (t, 1H), 8.24 (s, 1H), 8.12 (d, 1H), 7.79 (s, 1H), 7.67 (dd, 1H), 7.06 (m, 1H), 6.72 (t, 1H), 3.29 (m, 4H), 2.36 (m, 8H), 2.10 (s, 3H), 1.69 (t, 2H).

25

EXAMPLE 67

7-([(3-morpholin-4-yl)propyl]amino)methylpyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 1E, substituting 3-morpholinopropan-1-amine for cyclohexylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.22 (br s, 1H), 8.15 (s, 1H), 7.97 (d, 1H), 7.27 (s, 1H), 7.16 (d, 1H), 7.01 (m, 1H), 6.67 (m, 1H), 3.72 (s, 2H), 3.53 (m, 4H), 2.53 (t, 2H), 2.32 (m, 6H), 1.59 (t, 2H).

30

EXAMPLE 68

N-[2-(dimethylamino)ethyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting
5 N¹, N¹-dimethylethane-1,2-diamine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (400
MHz, DMSO-*d*₆) δ 11.35 (br s, 1H), 8.44 (t, 1H), 8.23 (m, 1H), 8.12 (d, 1H), 7.79 (s, 1H),
7.66 (dd, 1H), 7.06 (m, 1H), 6.73 (t, 1H), 3.38 (q, 2H), 2.43 (t, 2H), 2.20 (s, 6H).

EXAMPLE 69

10 7-{[(3-piperidin-1-ylpropyl)amino]methyl}pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 1E, substituting 3-
(piperidin-1-yl)propan-1-amine for cyclohexylamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ
11.22 (s, 1H), 8.17 (m, 1H), 7.99 (d, 1H), 7.34 (s, 1H), 7.20 (dd, 1H), 7.03 (m, 1H), 6.68
(t, 1H), 3.61 (s, 2H), 2.93 (s, 2H), 2.52 (m, 6H), 2.45 (m, 2H). 1.87 (m, 2H), 1.68 (m, 2H),
15 1.50 (m, 2H).

EXAMPLE 70

4-oxo-N-(3-piperidin-1-ylpropyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting
20 3-(piperidin-1-yl)propan-1-amine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (400 MHz,
DMSO-*d*₆) δ 11.37 (br s, 1H), 8.58 (t, 1H), 8.24 (s, 1H), 8.13 (d, 1H), 7.79 (s, 1H), 7.65
(dd, 1H), 7.06 (m, 1H), 6.73 (m, 1H), 3.30 (m, 2H), 2.32 (m, 6H), 1.69 (m, 2H), 1.48 (m,
4H), 1.38 (m, 2H).

25 EXAMPLE 71

7-{[(2-piperidin-1-ylethyl)amino]methyl}pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 1E, substituting 2-
(piperidin-1-yl)ethanamine for cyclohexylamine. The title compound was purified by RP-
HPLC eluting with 5/95 acetonitrile/0.1% TFA in water at 254 nm. The free base was
30 isolated after eluting from an ion exchange column (10 g). ¹H NMR (500 MHz, DMSO-
*d*₆) δ 11.21 (br s, 1H), 8.14 (m, 1H), 7.97 (d, 1H), 7.26 (s, 1H), 7.15 (d, 1H), 7.01 (m, 1H),
6.67 (m, 1H), 3.37 (s, 2H), 2.59 (t, 2H), 2.36 (t, 2H), 2.30 (m, 4H), 1.47 (m, 4H), 1.36 (m,
2H).

EXAMPLE 72

7-([4-(dimethylamino)cyclohexyl]amino)methylpyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 1E, substituting N¹,
5 N¹-dimethylcyclohexane-1,4-diamine for cyclohexylamine. The title compound was
purified by RP-HPLC eluting with 2/98 acetonitrile/0.1% TFA in water at 254 nm. The
free base was isolated after eluting from an ion exchange column (10 g). ¹H NMR (500
MHz, DMSO-*d*₆) δ 11.19 (br s, 1H), 8.14 (m, 1H), 7.96 (d, 1H), 7.29 (d, 1H), 7.18 (t, 1H),
7.01 (m, 1H), 6.67 (m, 1H), 3.73 (d, 2H), 2.16 (d, 6H), 2.10 (m, 2H), 1.95 (m, 1H), 1.77
10 (m, 1H), 1.68 (m, 2H), 1.43 (m, 2H), 1.08 (m, 2H).

EXAMPLE 73

4-oxo-N-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-
carboxamide

15 The title compound was prepared as described as in EXAMPLE 61E, substituting
2-amino-1-(pyrrolidin-1-yl)ethanone for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500
MHz, DMSO-*d*₆) δ 11.39 (s, 1H), 8.65 (t, 1H), 8.24 (m, 1H), 8.15 (d, 1H), 7.82 (s, 1H),
7.73 (d, 1H), 7.07 (m, 1H), 6.73 (m, 1H), 4.04 (d, 2H), 3.49 (t, 2H), 3.31 (t, 2H), 1.92 (p,
2H), 1.79 (p, 2H).

20

EXAMPLE 74

N-[4-(dimethylamino)cyclohexyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-
carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting
25 N¹,N¹-dimethylcyclohexane-1,4-diamine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR
(500 MHz, DMSO-*d*₆) δ 8.33 (br s, 1H), 8.29 (d, 1H), 8.24 (m, 1H), 8.10 (m, 1H), 7.78 (s,
1H), 7.69 (d, 1H), 7.07 (m, 1H), 6.73 (m, 1H), 3.74 (m, 1H), 2.22 (s, 6H), 2.19 (m, 1H),
1.90 (m, 2H), 1.85 (m, 2H), 1.34 (m, 4H).

30

EXAMPLE 75

4-oxo-N-[3-(piperidin-1-ylsulfonyl)phenyl]-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-
carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting 3-(piperidin-1-ylsulfonyl)aniline for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.46 (s, 1H), 10.67 (s, 1H), 8.30 (m, 1H), 8.24 (m, 2H), 8.13 (d, 1H), 7.87 (m, 2H), 7.64 (t, 1H), 7.45 (d, 1H), 7.10 (m, 1H), 6.76 (m, 1H), 2.93 (m, 4H), 1.56 (m, 4H), 1.39 (m, 2H).

EXAMPLE 76

7-((2-oxo-2-(pyrrolidin-1-yl)ethylamino)methyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 1E, substituting 2-amino-1-(pyrrolidin-1-yl)ethanone for cyclohexylamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.23 (s, 1H), 8.16 (s, 1H), 7.99 (d, 1H), 7.31 (s, 1H), 7.21 (d, 1H), 7.02 (m, 1H), 6.68 (m, 1H), 3.70 (s, 2H), 3.34 (s, 2H), 3.21 (m, 6H), 1.72 (m, 2H).

EXAMPLE 77

4-oxo-N-(pyridin-4-ylmethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting pyridin-4-ylmethanamine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.40 (s, 1H), 9.21 (t, 1H), 8.52 (m, 2H), 8.26 (s, 1H), 8.17 (d, 1H), 7.85 (s, 1H), 7.78 (dd, 1H), 7.34 (d, 2H), 7.07 (m, 1H), 6.74 (m, 1H), 4.52 (d, 2H).

EXAMPLE 78

4-oxo-N-(2-thiomorpholin-4-ylethyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting 2-thiomorpholinoethanamine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.39 (s, 1H), 8.46 (t, 1H), 8.24 (s, 1H), 8.13 (d, 1H), 7.78 (s, 1H), 7.65 (dd, 1H), 7.06 (m, 1H), 6.73 (m, 1H), 3.38 (m, 2H), 2.73 (m, 4H), 2.62 (m, 4H), 2.53 (m, 2H).

EXAMPLE 79

N,N-dimethyl-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting dimethylamine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ

11.32 (br s, 1H), 8.23 (s, 1H) 8.09 (d, 1H), 7.32 (s, 1H), 7.25 (dd, 1H), 7.06 (m, 1H), 6.72 (m, 1H), 2.99 (br s, 3H), 2.96 (br s, 3H).

EXAMPLE 80

5 N-(1-ethylpiperidin-3-yl)-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting 1-ethylpiperidin-3-amine for 2-(pyrrolidin-1-yl)ethanamine. The title compound was isolated after purification on silica gel (15 g) eluting with 10/90 2M ammonia in methanol/methylene chloride. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.35 (s, 1H), 8.25 (m, 10 2H) 8.12 (d, 1H) 7.79 (s, 1H), 7.69 (dd, 1H), 7.06 (m, 1H), 6.73 (m, 1H), 3.94 (m, 1H), 2.93 (m, 1H), 2.77 (m, 1H), 2.38 (m 2H), 1.83 (m, 4H), 1.53 (m, 1H), 1.38 (, 1H), 1.01 (t, 3H).

EXAMPLE 81

15 4-oxo-N-(4-phenylbutyl)-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting 4-phenylbutan-1-amine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.36 (s, 1H), 8.54 (t, 1H), 8.24 (s, 1H), 8.11 (d, 1H) 7.78 (s, 1H), 7.66 (dd, 1H), 7.26 (m, 2H), 7.22 (m, 3H), 7.07 (m, 1H), 6.72 (m, 1H), 3.30 (q, 2H) 2.62 (t, 2H) 1.60 (m, 20 4H).

EXAMPLE 82

7-(pyrrolidin-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described as in EXAMPLE 61E, substituting 25 pyrrolidine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.22 (m, 1H), 8.08 (d, 1H), 7.45 (s, 1H), 7.37 (dd, 1H) 7.06 (m, 1H), 6.72 (m, 1H), 3.46 (m 4H), 1.86 (m, 4H).

EXAMPLE 83

30 N-[4-(4-benzylpiperazin-1-yl)phenyl]-4-oxo-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting 4-(4-benzylpiperazin-1-yl)aniline for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (300 MHz,

DMSO-*d*₆) δ 11.00 (s, 1H) 9.78 (s, 1H) 8.08 (s, 1H), 7.99 (d, 1H), 7.80 (s, 1H), 7.70 (d, 1H), 7.50 (d, 2H), 7.26 (m, 5H), 7.00 (m, 1H), 6.82 (d, 2H) 6.63 (t, 1H), 3.49 (s, 2H), 3.07 (m, 4H), 2.49 (m, 2H) 2.41 (m, 2H).

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EXAMPLE 84

4-oxo-N-1,3-thiazol-2-yl-4,5-dihydropyrrolo[1,2-a]quinoxaline-7-carboxamide

The title compound was prepared as described as in EXAMPLE 61E, substituting thiazol-2-amine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.15 (br s, 1H), 8.16 (m, 1H), 8.10 (d, 1H), 7.97 (m, 3H), 7.52 (d, 1H), 7.21 (d, 1H), 7.07 (m, 1H), 6.72 (m, 1H).

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EXAMPLE 85

7-(piperidin-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described as in EXAMPLE 61E, substituting piperidine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.32 (br s, 1H), 8.21 (m, 1H), 8.09 (d, 1H), 7.29 (s, 1H), 7.20 (dd, 1H), 7.06 (m, 1H), 6.71 (m, 1H), 3.40 (m, 4H), 1.64 (m, 2H), 1.53 (m, 4H).

15

EXAMPLE 86

20 7-[(4-aminopiperidin-1-yl)methyl]pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 1E, substituting *tert*-butyl piperidin-4-ylcarbamate for cyclohexylamine. The crude mixture was concentrated and dissolved in 2 mL 1:1 TFA:methylene chloride. After stirring for 12 hours, the mixture was concentrated and purified by RP-HPLC eluting with 10/90 acetonitrile/0.1 % TFA in water at 254 nm. The free base was isolated after eluting from an ion exchange column (10 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (m, 1H), 7.97 (d, 1H) 7.24 (m, 1H), 7.10 (dd, 1H) 7.01 (m, 1H), 6.67 (m, 1H), 3.45 (s, 2H) 3.31 (br s, 2H), 2.73 (m, 2H), 2.57 (m, 1H), 1.96 (t, 2H), 1.67 (br d, 2H) 1.27 (m, 2H).

25

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EXAMPLE 87

7-[(4-aminopiperidin-1-yl)carbonyl]pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described as in EXAMPLE 61E, substituting *tert*-butyl piperidin-4-ylcarbamate for 2-(pyrrolidin-1-yl)ethanamine. The crude mixture

was concentrated and dissolved in 2 mL 1:1 TFA:methylene chloride. After stirring for 12 hours, the mixture was concentrated and purified by RP-HPLC eluting with 10/90 acetonitrile/0.1 % TFA in water at 254 nm. The title compound was isolated as the free base after eluting from an ion exchange column (10 g). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.22 (s, 1H), 8.10 (d, 1H), 7.30 (s, 1H), 7.20 (d, 1H), 7.06 (m, 1H), 6.72 (m, 1H), 4.27 (br s, 2H), 3.05 (m, 4H), 2.86 (m, 1H), 1.76 (m, 2H), 1.20 (m, 2H).

EXAMPLE 88

7-(1,4-diazepan-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as a TFA salt as described as in EXAMPLE 61, substituting *tert*-butyl 1,4-diazepane-1-carboxylate for 2-(pyrrolidin-1-yl)ethanamine. The crude mixture was concentrated and dissolved in 2 mL 1:1 TFA:methylene chloride. After stirring for 12 hours, the mixture was concentrated and purified by RP-HPLC eluting with 10/90 acetonitrile/0.1 % TFA in water at 254nm. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.40 (s, 1H), 8.94 (br s, 1H), 8.23 (s, 1H), 8.12 (d, 1H), 7.34 (s, 1H), 7.29 (d, 1H), 7.07 (m, 1H), 6.73 (m, 1H), 3.84 (m, 1H), 3.64 (m, 2H), 3.49 (m, 1H), 3.23 (m, 4H), 1.98 (m, 2H).

EXAMPLE 89

6-(pyrrolidin-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

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EXAMPLE 89A

The title compound was prepared as described in EXAMPLE 34A, substituting methyl 1H-pyrrole-2-carboxylate for ethyl pipercolinate and substituting 1-bromo-3-fluoro-2-nitrobenzene for 4-fluoro-3-nitro-benzoic acid. MS (ESI) *m/e* 324 (M+H)⁺.

25

EXAMPLE 89B

EXAMPLE 89A (577 mg), dichloro[1,1'-ferrocenylbis(diphenylphosphine)]palladium(II) dichloromethane (80 mg), and triethylamine (0.5 mL) were dissolved in 50 mL methanol. The mixture was heated at 100° C under 60 psi of carbon monoxide for 3 hours. The mixture was filtered through Celite to remove the catalyst. The title compound was isolated after purification on silica gel (40 g) eluting with 1:4 ethyl acetate:hexane. MS (ESI) *m/e* 242 (M+H)⁺.

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EXAMPLE 89C

EXAMPLE 89 B (45 mg) was dissolved in 3 mL 5:1 THF:methanol and 1 mL 1M lithium hydroxide was added. After stirring for 12 hours, the mixture was neutralized with 2M HCl. The resultant solid was collected and dried. MS (ESI) m/e 228 (M+H)⁺.

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EXAMPLE 89D

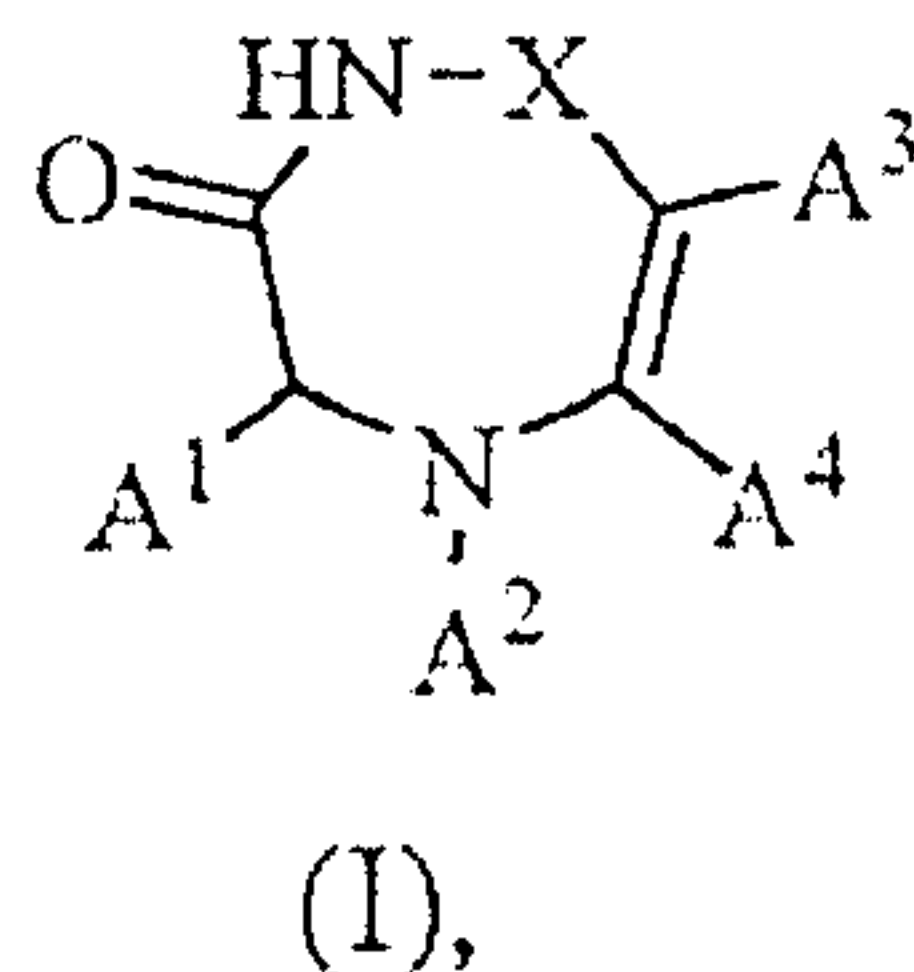
6-(pyrrolidin-1-ylcarbonyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one

The title compound was prepared as described in EXAMPLE 61E, substituting EXAMPLE 89C for EXAMPLE 61D and substituting pyrrolidine for 2-(pyrrolidin-1-yl)ethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 8.23 (s, 1H), 8.15 (d, 1H) 10 7.38 (m, 1H), 7.27 (d, 1H), 7.08 (m, 1H), 6.72 (m, 1H), 3.56 (t, 2H), 3.32 (t, 2H), 1.86 (m, 4H).

The foregoing is meant to be illustrative of the invention and not meant to limit it 15 to disclosed embodiments. Variations and changes obvious to one skilled in the art are intended to be within the scope and nature of the invention as defined in the appended claims.

WE CLAIM:

1. A compound having formula I

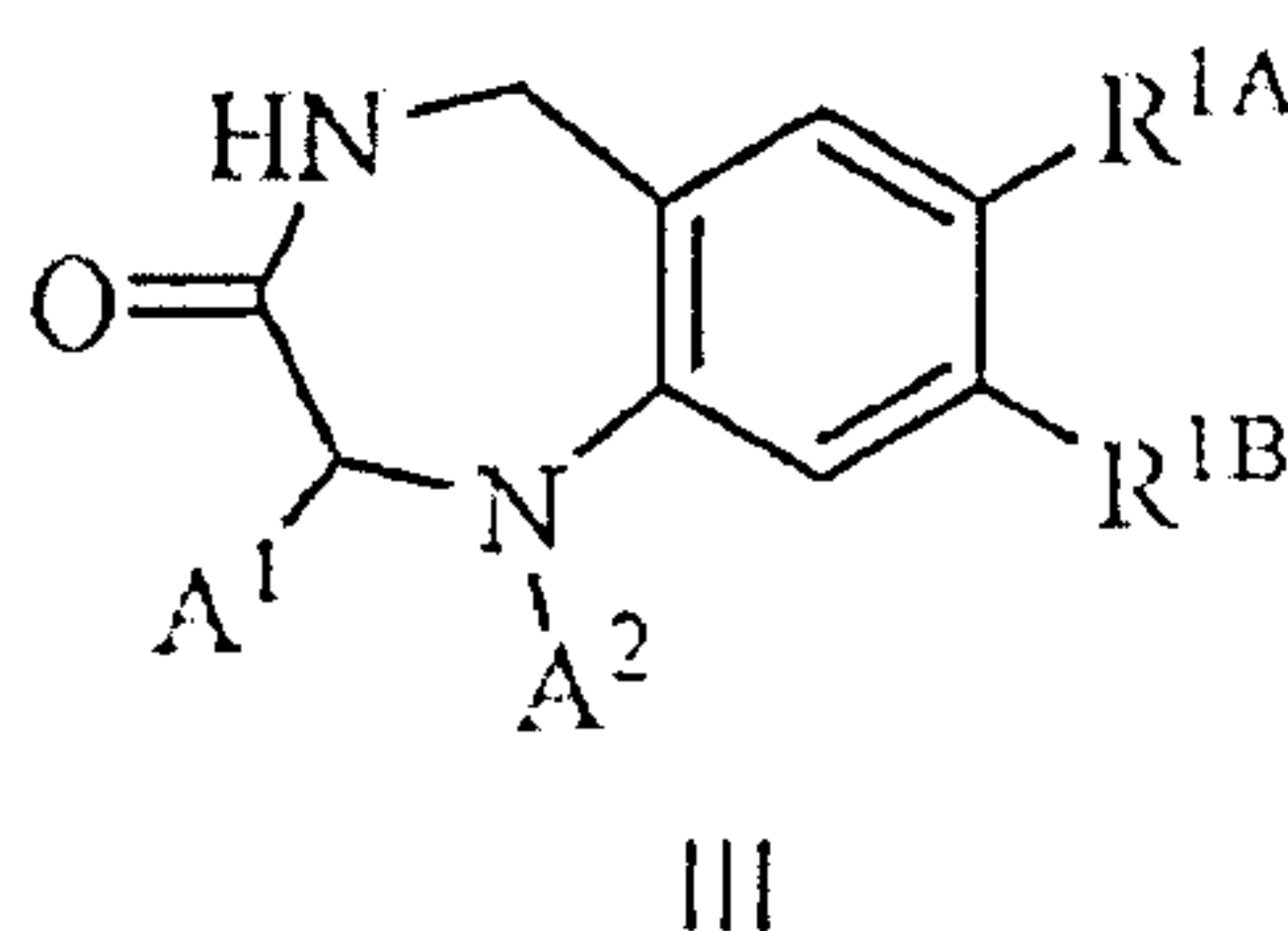


or a salt thereof, wherein

X is CH₂;

A¹ and A², together with the atoms to which they are attached, are pyrrole, imidazole, piperidine, or pyrrolidine;

A³ and A⁴, together with the atoms to which they are attached, are benzene which is substituted with R^{1A} and R^{1B} as described in Formula III



one of R^{1A} and R^{1B} is H, and the other is R¹, C(O)R¹, C(O)NHR¹, or C(O)N(R¹)₂;

R¹ is R², R³, R⁴ or R⁵;

R² is phenyl;

R³ is heteroarene;

R⁴ is cycloalkyl or heterocycloalkyl;

R⁵ is alkyl which is unsubstituted or substituted with one or two of independently selected R⁶, NHR⁶, N(R⁶)₂, C(O)R⁶, R⁶C(O)R⁶ or NR⁶S(O)₂R⁶;

R^6 is R^7 , R^8 , R^9 or R^{10} ;

R^7 is phenyl;

R^8 is heteroarene;

R^9 is cycloalkyl or heterocycloalkyl;

R^{10} is alkyl which is unsubstituted or substituted with one or two of independently selected R^{11} , $C(O)OH$, $N(R^{11})_2$, $C(O)R^{11}$ or $C(O)OR^{11}$;

R^{11} is R^{12} , R^{14} or R^{14A} ;

R^{12} is phenyl;

R^{14} is cycloalkyl or heterocycloalkyl;

R^{14A} is alkyl;

wherein the moieties represented by R^2 , R^4 and R^9 are independently unsubstituted or independently substituted with R^{15} , SO_2R^{15} , NH_2 , $N(R^{15})_2$ or (O);

wherein R^{15} is R^{18} or R^{19} ;

R^{18} is heterocycloalkyl which is independently unsubstituted or substituted with alkyl which is unsubstituted or substituted with one or two of phenyl;

and

R^{19} is alkyl.

2. The compound of claim 1 that is:

8-((dimethylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one;

8-(pyrrolidin-1-ylmethyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one;

8-((isopropylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one;

8-((4-methylpiperazin-1-yl)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one;

8-(((2-ethoxyethyl)(methyl)amino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a]
[1,4]benzodiazepin-4-one;

8-(((cyclohexylmethyl)amino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a]
[1,4]benzodiazepin-4-one;

8-((benzylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one;

8-((cyclopentylamino)methyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-
one;

8-(piperidin-1-ylmethyl)-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one; or

8-[(cyclohexylamino)methyl]-5,6-dihydro-4H-pyrrolo[1,2-a][1,4]benzodiazepin-4-one.

3. A pharmaceutical composition comprising a compound of claim 1 or claim 2 and a pharmaceutically acceptable excipient.
4. Use of a compound of claim 1 or claim 2 for treatment of cancer in a mammal.
5. Use of a compound of claim 1 or claim 2 for decreasing tumor volume in a mammal.
6. Use of a compound of claim 1 or claim 2 in combination with radiotherapy for treatment of cancer in a mammal.
7. Use of a compound of claim 1 or claim 2 in combination with a chemotherapeutic agent, for treatment of cancer, wherein the chemotherapeutic agent is emozolomide, dacarbazine, cyclophosphamide, carmustine, melphalan, lomustine, carboplatin, cisplatin, 5-FU +/- leucovorin, gemcitabine, methotrexate, bleomycin, irinotecan, camptothecin, or topotecan.
8. Use of a compound of claim 1 or claim 2 in the manufacture of a medicament for treatment of cancer.
9. Use of a compound of claim 1 or claim 2 in the manufacture of a medicament for decreasing tumor volume.