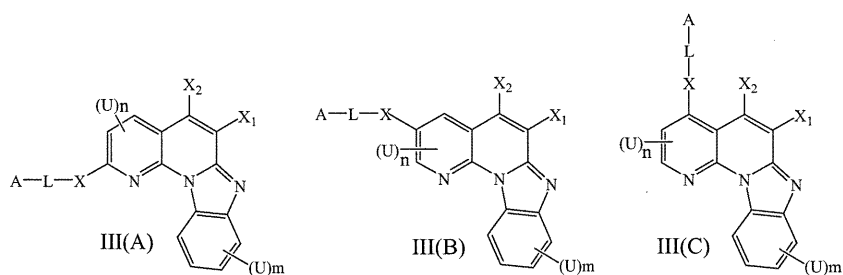


SUMMARY

[006] Disclosed herein are novel compounds and methods of treating or preventing any one of the diseases or conditions described herein comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, to a mammal in need thereof. In specific examples, the compound inhibits ribosome biogenesis by inhibiting POL1 transcription and the disease or condition is amenable to treatment or prevention by the inhibition of POL1 transcription.

[007] In one aspect, the present invention refers to a compound having the Formula III(A), III(B) or



III(C): , or a pharmaceutically

acceptable salt thereof; wherein L is a bond, C₁-C₁₀ alkylene, C₁-C₁₀ heteroalkylene, C₂-C₁₀ alkenylene or C₂-C₁₀ heteroalkenylene linker, each of which is optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C₁-C₆ alkyl; A is heterocycloalkyl, heteroaryl, quaternary amine or NR₄R₅, wherein R₄ and R₅ are independently H, optionally substituted C₁-C₈ alkyl, C₂-C₈ heteroalkyl, C₂-C₈ alkenyl, C₂-C₈ heteroalkenyl, C₂-C₈ alkynyl, C₂-C₈ heteroalkynyl, C₁-C₈ acyl, C₂-C₈ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₂ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl group, wherein R₄ and R₅ are optionally linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and wherein each R₄ and R₅ groups is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')₂, SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR', CON(R')₂, OOCR', COR', and NO₂, wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₆ acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S; X is NR₆, O, or S, wherein R₆ is H, optionally substituted C₁-C₈ alkyl, C₂-C₈ heteroalkyl, C₂-C₈ alkenyl, C₂-C₈ heteroalkenyl, C₂-C₈ alkynyl, C₂-C₈ heteroalkynyl, C₁-C₈ acyl, C₂-C₈ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₂ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl group, wherein R₆ is optionally linked to R₄ or R₅ to form a 3-8 membered ring substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')₂,

1 SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR', CON(R')₂, OOCR',
 2 COR', and NO₂, wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl, C₂-C₆
 3 heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which is
 4 optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₆
 5 acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered
 6 ring optionally containing up to three heteroatoms selected from N, O and S; X₁ is an optionally
 7 substituted C₁-C₈ alkyl, C₂-C₈ heteroalkyl, C₂-C₈ alkenyl, C₂-C₈ heteroalkenyl, C₂-C₈ alkynyl, C₂-C₈
 8 heteroalkynyl, C₁-C₈ acyl, C₂-C₈ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₂ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂
 9 heteroarylalkyl group, or X₁ is H, NR₂R₃, SOR₂, SO₂R₂, SO₂NR₂R₃, NR₂SO₂R₃, NR₂CONR₂R₃,
 10 NR₂COOR₃, NR₂COR₃, CN, COOR₂, ester bioisostere, COOH, carboxy bioisostere, CONR₂R₃, amide
 11 bioisostere, OOCR₂, COR₂, or NO₂; X₂ is H, halogen, CF₃, CN, OR₇, NR₈R₉, SR₇, SO₂NR₈R₉, C₁-C₁₀
 12 alkyl, C₁-C₁₀ heteroalkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ heteroalkenyl, each of which is optionally substituted
 13 with one or more halogens, O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic
 14 ring; wherein each R₇, R₈ and R₉ is independently selected from H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆
 15 acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of
 16 which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR',
 17 OR', N(R')₂, SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR',
 18 CON(R')₂, OOCR', COR', and NO₂; wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl,
 19 C₁-C₆ acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl,
 20 each of which is optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄
 21 heteroalkyl, C₁-C₆ acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form
 22 a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S, wherein R₇
 23 is not hydrogen when X₂ is OR₇, and (U)_n and (U)_m are independently H, halogen, CF₃, CN, OR₇, NR₈R₉,
 24 SR₇, SO₂NR₈R₉, C₁-C₁₀ alkyl, C₁-C₁₀ heteroalkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ heteroalkenyl, each of which
 25 is optionally substituted with one or more halogens, O, or an optionally substituted 3-7 membered
 26 carbocyclic or heterocyclic ring; wherein R₂ and R₃ groups on the same atom or on adjacent atoms are
 27 linked to form a 3-8 membered ring, optionally containing one or more N, O or S and each independently
 28 optionally substituted with one or more substituents selected from =O, =N-CN, =N-OR', =NR', OR',
 29 N(R')₂, SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR', CON(R')₂,
 30 OOCR', COR', and NO₂, wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl,
 31 C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which
 32 is optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-
 33 C₆ acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7
 34 membered ring optionally containing up to three heteroatoms selected from N, O and S. In another aspect,

the present invention refers to the compound of Claim 1, having the Formula III(A) or Formula III(B), wherein; L is a bond or C₁-C₁₀ alkylene; A is a heterocycloalkyl group or NR₄R₅, wherein R₄ and R₅ are independently H or an optionally substituted C₁-C₈ alkyl or C₂-C₈ heteroalkyl group; R₄ and R₅ are linked to form a 3-8 membered ring, optionally containing one or more N or O atom; and each R₄ and R₅ groups is optionally substituted with one or more substituents; and X is NR₆, wherein R₆ is H or a C₁-C₈ alkyl group, wherein R₆ is optionally linked to R₄ or R₅ to form a 3-8 membered ring substituted with one or more substituents. In yet another aspect, the present invention refers to the compound of Claim 2, X₂ is H and X₁ is CONR₂R₃, wherein R₂ and R₃ are independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ heteroalkyl, C₂-C₁₀ alkenyl, and C₂-C₁₀ heteralkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring. In one example, described herein is a method for treating or preventing cancer in a mammal comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal in need thereof. In another example, described herein is a method for treating or preventing an inflammatory disease in a mammal comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal in need thereof.

[008] In still another example, described herein is a method for treating or preventing a proliferative disorder in a mammal comprising administering a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal in need thereof. In another example, described herein is a method for treating or preventing a disease or disorder in a mammal comprising administering a therapeutically effective amount of a compound described herein, wherein the compound inhibits ribosome biogenesis by inhibiting POL1 transcription.

[009] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

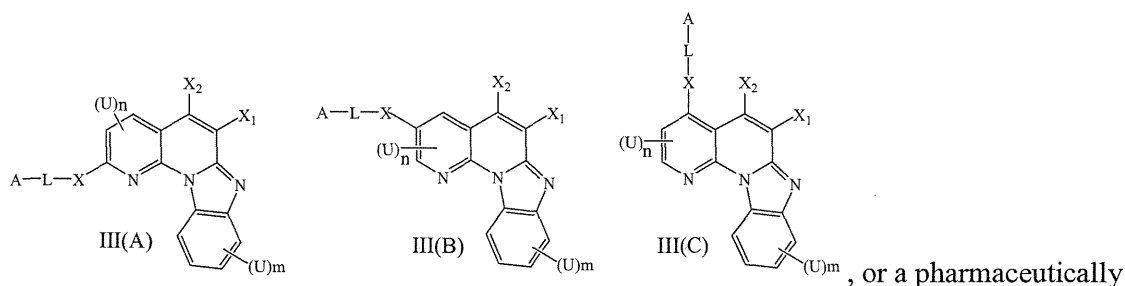
Compounds

[010] Compounds described herein, including pharmaceutically acceptable salts, prodrugs, active metabolites and pharmaceutically acceptable solvates thereof, inhibit ribosome biogenesis

CLAIMS

WHAT IS CLAIMED IS:

1. A compound having the Formula III(A), III(B) or III(C):



acceptable salt thereof; wherein

L is a bond, C₁-C₁₀ alkylene, C₁-C₁₀ heteroalkylene, C₂-C₁₀ alkenylene or C₂-C₁₀ heteroalkenylene linker, each of which is optionally substituted with one or more substituents selected from the group consisting of halogen, oxo (=O), or C₁-C₆ alkyl;

A is heterocycloalkyl, heteroaryl, quaternary amine or NR₄R₅,

wherein R₄ and R₅ are independently H, optionally substituted C₁-C₈ alkyl, C₂-C₈ heteroalkyl, C₂-C₈ alkenyl, C₂-C₈ heteroalkenyl, C₂-C₈ alkynyl, C₂-C₈ heteroalkynyl, C₁-C₈ acyl, C₂-C₈ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₂ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl group,

wherein R₄ and R₅ are optionally linked to form a 3-8 membered ring, optionally containing one or more N, O or S; and

wherein each R₄ and R₅ groups is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')₂, SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR', CON(R')₂, OOCR', COR', and NO₂,

wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₆ acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O;

wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X is NR₆, O, or S,

wherein R₆ is H, optionally substituted C₁-C₈ alkyl, C₂-C₈ heteroalkyl, C₂-C₈ alkenyl, C₂-C₈ heteroalkenyl, C₂-C₈ alkynyl, C₂-C₈ heteroalkynyl, C₁-C₈ acyl, C₂-C₈ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₂ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl group,

wherein R₆ is optionally linked to R₄ or R₅ to form a 3-8 membered ring substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')₂, SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR', CON(R')₂, OOCR', COR', and NO₂,

wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₆ acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

X₁ is an optionally substituted C₁-C₈ alkyl, C₂-C₈ heteroalkyl, C₂-C₈ alkenyl, C₂-C₈ heteroalkenyl, C₂-C₈ alkynyl, C₂-C₈ heteroalkynyl, C₁-C₈ acyl, C₂-C₈ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₂ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl group, or

X₁ is H, NR₂R₃, SOR₂, SO₂R₂, SO₂NR₂R₃, NR₂SO₂R₃, NR₂CONR₂R₃, NR₂COOR₃, NR₂COR₃, CN, COOR₂, ester bioisostere, COOH, carboxy bioisostere, CONR₂R₃, amide bioisostere, OOCR₂, COR₂, or NO₂;

X₂ is H, halogen, CF₃, CN, OR₇, NR₈R₉, SR₇, SO₂NR₈R₉, C₁-C₁₀ alkyl, C₁-C₁₀ heteroalkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ heteroalkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring; wherein each R₇, R₈ and R₉ is independently selected from H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')₂, SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR', CON(R')₂, OOCR', COR', and NO₂; wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₆ acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O; wherein two R' can be

linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S, wherein R₇ is not hydrogen when X₂ is OR₇, and (U)_n and (U)_m are independently H, halogen, CF₃, CN, OR₇, NR₈R₉, SR₇, SO₂NR₈R₉, C₁-C₁₀ alkyl, C₁-C₁₀ heteroalkyl, C₂-C₁₀ alkenyl, or C₂-C₁₀ heteroalkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring; wherein R₂ and R₃ groups on the same atom or on adjacent atoms are linked to form a 3-8 membered ring, optionally containing one or more N, O or S and each independently optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', N(R')₂, SR', SO₂R', SO₂NR'₂, NR'SO₂R', NR'CONR'₂, NR'COOR', NR'COR', CN, COOR', CON(R')₂, OOCR', COR', and NO₂, wherein each R' is independently H, C₁-C₆ alkyl, C₂-C₆ heteroalkyl, C₁-C₆ acyl, C₂-C₆ heteroacyl, C₆-C₁₀ aryl, C₅-C₁₀ heteroaryl, C₇-C₁₂ arylalkyl, or C₆-C₁₂ heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C₁-C₄ alkyl, C₁-C₄ heteroalkyl, C₁-C₆ acyl, C₁-C₆ heteroacyl, hydroxy, amino, and =O; wherein two R' can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S.

2. The compound of Claim 1, having the Formula III(A) or Formula III(B), wherein;

L is a bond or C₁-C₁₀ alkylene;

A is a heterocycloalkyl group or NR₄R₅,

wherein R₄ and R₅ are independently H or an optionally substituted C₁-C₈ alkyl or C₂-C₈ heteroalkyl group; or

R₄ and R₅ are linked to form a 3-8 membered ring, optionally containing one or more N or O atom; and each R₄ and R₅ groups is optionally substituted with one or more substituents; and

X is NR₆,

wherein R₆ is H or a C₁-C₈ alkyl group, wherein R₆ is optionally linked to R₄ or R₅ to form a 3-8 membered ring substituted with one or more substituents.

3. The compound of Claim 2, wherein X₂ is H and X₁ is CONR₂R₃, wherein R₂ and R₃ are independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ heteroalkyl, C₂-C₁₀ alkenyl, and C₂-C₁₀ heteroalkenyl, each of which is optionally substituted with one or more halogens, =O, or an optionally substituted 3-7 membered carbocyclic or heterocyclic ring.