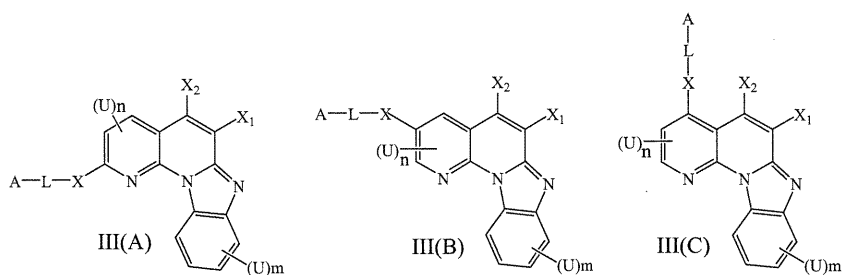


SUMMARY

[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): 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,

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

17 **[008]** In still another example, described herein is a method for treating or preventing a proliferative
18 disorder in a mammal comprising administering a therapeutically effective amount of a compound
19 described herein, or a pharmaceutically acceptable salt, or solvate thereof, to the mammal in need thereof.
20 In another example, described herein is a method for treating or preventing a disease or disorder in a
21 mammal comprising administering a therapeutically effective amount of a compound described herein,
22 wherein the compound inhibits ribosome biogenesis by inhibiting POL1 transcription.

23 **[009]** Other objects, features and advantages of the compounds, methods and compositions described
24 herein will become apparent from the following detailed description. It should be understood, however,
25 that the detailed description and the specific examples, while indicating specific embodiments, are given
26 by way of illustration only, since various changes and modifications within the spirit and scope of the
27 instant disclosure will become apparent to those skilled in the art from this detailed description.

28 DETAILED DESCRIPTION OF THE INVENTION

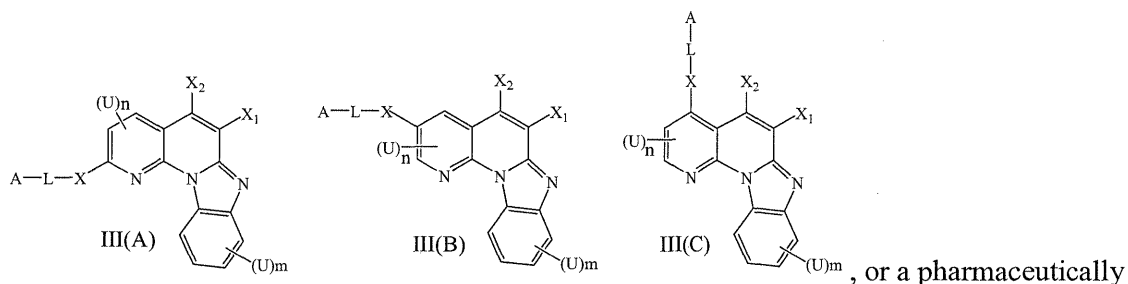
29 Compounds

30 **[010]** Compounds described herein, including pharmaceutically acceptable salts, prodrugs, active
31 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

1 linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected
2 from N, O and S, wherein R_7 is not hydrogen when X_2 is OR_7 , and
3 $(U)_n$ and $(U)_m$ are independently H, halogen, CF_3 , CN, OR_7 , NR_8R_9 , SR_7 , $SO_2NR_8R_9$, C_1-C_{10}
4 alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, or C_2-C_{10} heteroalkenyl, each of which is optionally
5 substituted with one or more halogens, $=O$, or an optionally substituted 3-7 membered
6 carbocyclic or heterocyclic ring;
7 wherein R_2 and R_3 groups on the same atom or on adjacent atoms are linked to form a 3-8
8 membered ring, optionally containing one or more N, O or S and each independently
9 optionally substituted with one or more substituents selected from halo, $=O$, $=N-CN$, $=N-$
10 OR' , $=NR'$, OR' , $N(R')_2$, SR' , SO_2R' , $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'COOR'$,
11 $NR'COR'$, CN, $COOR'$, $CON(R')_2$, $OOOR'$, COR' , and NO_2 ,

12 wherein each R' is independently H, C_1-C_6 alkyl, C_2-C_6 heteroalkyl, C_1-C_6 acyl, C_2-C_6
13 heteroacyl, C_6-C_{10} aryl, C_5-C_{10} heteroaryl, C_7-C_{12} arylalkyl, or C_6-C_{12} heteroarylalkyl,
14 each of which is optionally substituted with one or more groups selected from halo, C_1-
15 C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_6 acyl, C_1-C_6 heteroacyl, hydroxy, amino, and $=O$;
16 wherein two R' can be linked to form a 3-7 membered ring optionally containing up to
17 three heteroatoms selected from N, O and S.

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

19 L is a bond or C_1-C_{10} alkylene;

20 A is a heterocycloalkyl group or NR_4R_5 ,

21 wherein R_4 and R_5 are independently H or an optionally substituted C_1-C_8 alkyl or C_2-C_8
22 heteroalkyl group; or

23 R_4 and R_5 are linked to form a 3-8 membered ring, optionally containing one or more N or O
24 atom; and each R_4 and R_5 groups is optionally substituted with one or more substituents; and

25 X is NR_6 ,

26 wherein R_6 is H or a C_1-C_8 alkyl group, wherein R_6 is optionally linked to R_4 or R_5 to
27 form a 3-8 membered ring substituted with one or more substituents.

28 3. The compound of Claim 2, wherein X_2 is H and X_1 is $CONR_2R_3$, wherein R_2 and R_3 are
29 independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, and C_2-C_{10}
30 heteroalkenyl, each of which is optionally substituted with one or more halogens, $=O$, or an
31 optionally substituted 3-7 membered carbocyclic or heterocyclic ring.
32