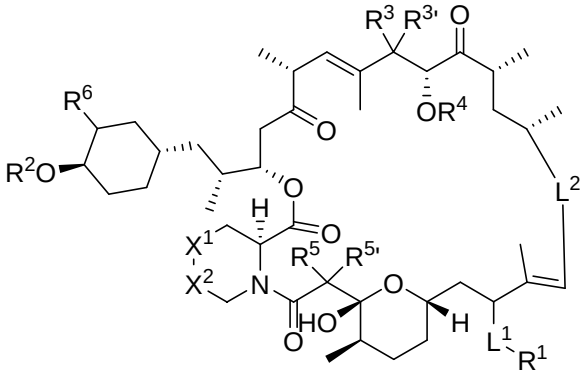
CLAIMS

We claim:

1. A compound of Formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

L^1 is a covalent bond, or a C_{1-30} bivalent straight or branched saturated or unsaturated hydrocarbon chain, wherein 1-10 methylene units of the chain are independently and optionally replaces with $-Cy_1-$, -O-, -S-, $-S(O)_2-$, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-CF_2-$, -P(O)(R)-, $-Si(R)_2-$, -Si(OR)(R)-, or -NR-;

each $-Cy_1-$ is independently an optionally substituted bivalent ring selected from phenylene, 4-7 membered saturated or partially unsaturated heterocyclylene having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroarylene having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

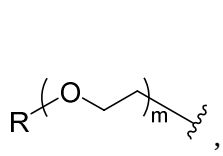
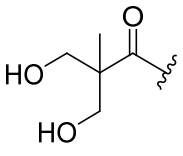
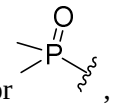
two R groups on the same atom are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms, in additional to the same atom to which they are attached, independently selected from nitrogen, oxygen, or sulfur;

L^2 is a C_{1-6} bivalent straight or branched saturated or unsaturated hydrocarbon chain, wherein 1-2 methylene units of the chain are independently and optionally replaced with $-Cy_1-$;

R^1 is hydrogen, halogen, -OR, -CN, $-NO_2$, $-NR_2$, or an optionally substituted group selected from a C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered saturated or partially unsaturated

bicyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfurs, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

wherein $-L^1-R^1$ taken together do not form -OMe;

R^2 is , , or ,

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

R^3 is hydrogen, halogen; -OR, or $-OSiR_3$;

$R^{3'}$ is hydrogen,

or R^3 and $R^{3'}$ are taken together to form =O or =S;

R^4 is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic;

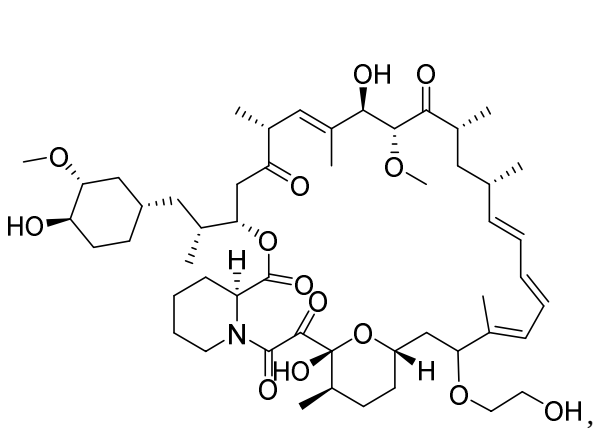
R^5 and $R^{5'}$ are each hydrogen or taken together to form =O;

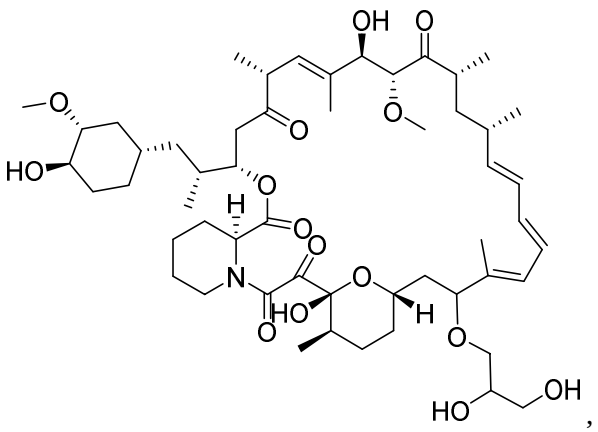
R^6 is hydrogen, -OMe, or halogen; and

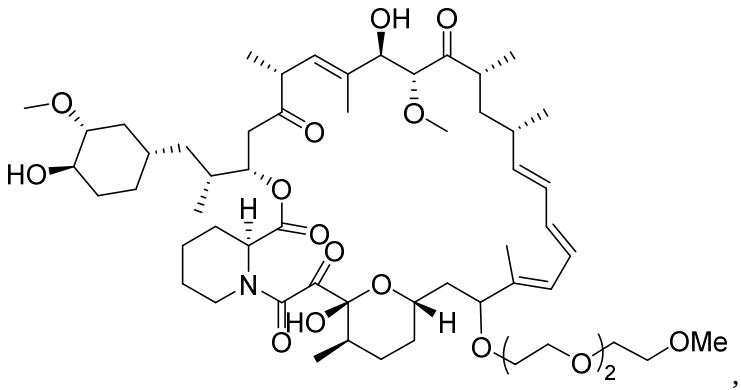
X^1 and X^2 are each independently $-CH_2-$, -S-, or -S(O)-,

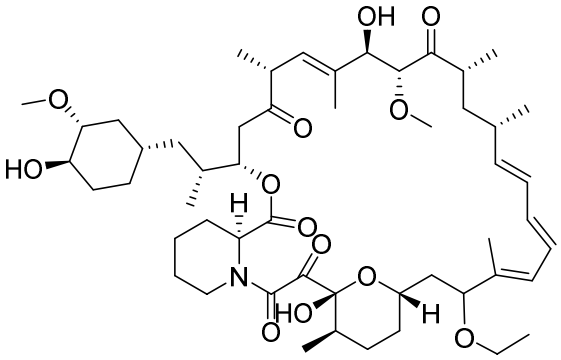
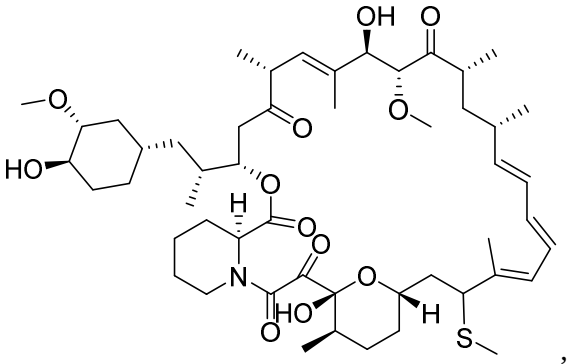
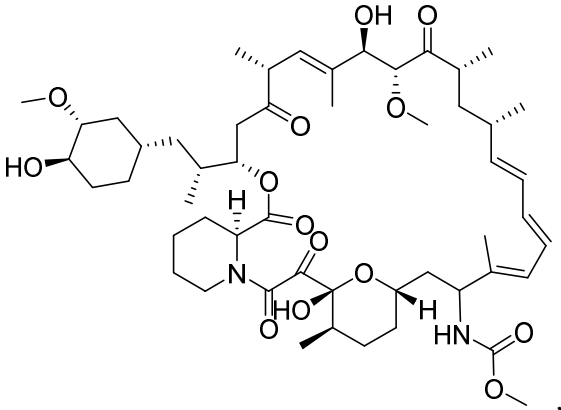
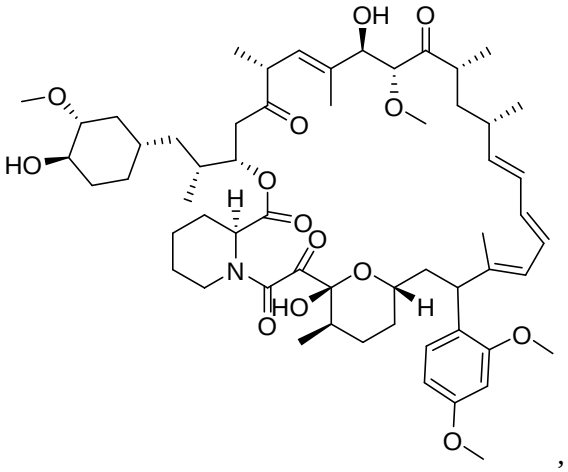
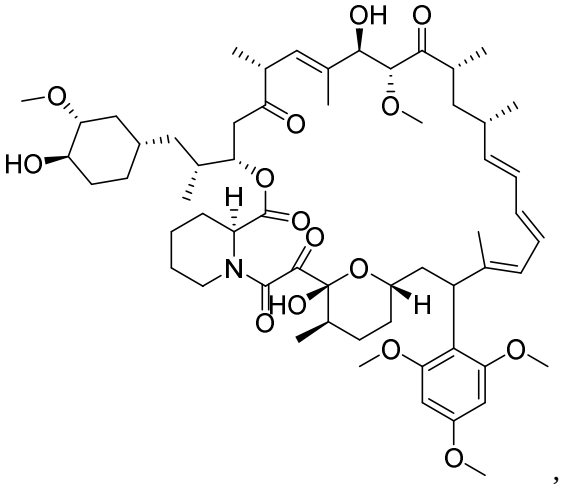
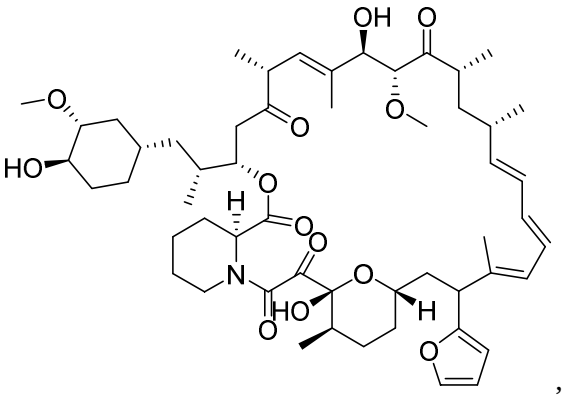
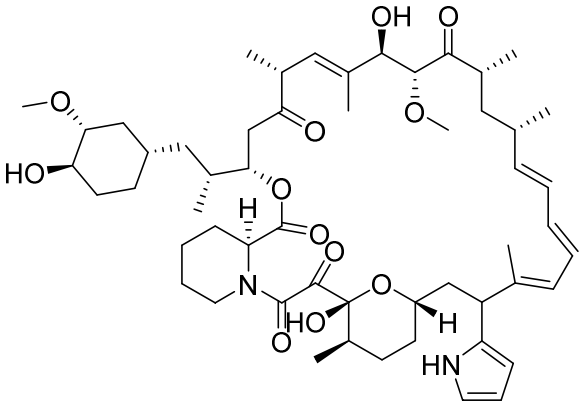
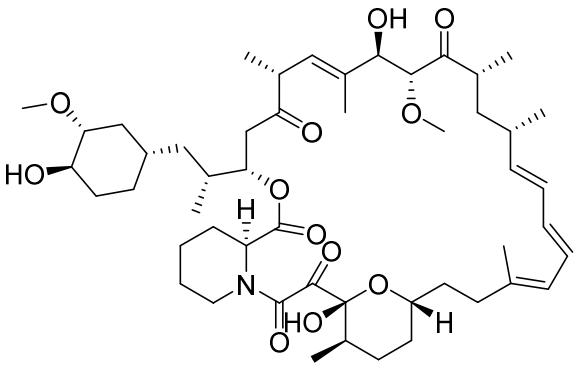
wherein at least one of X^1 and X^2 is $-CH_2-$,

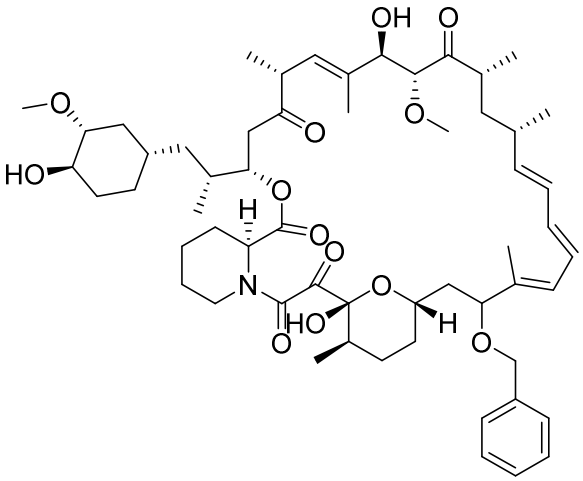
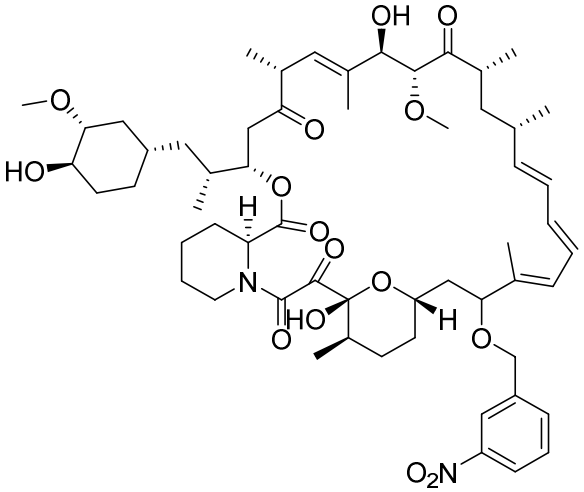
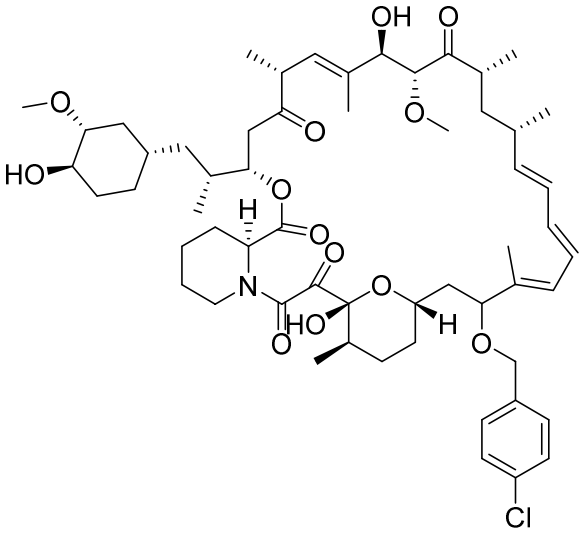
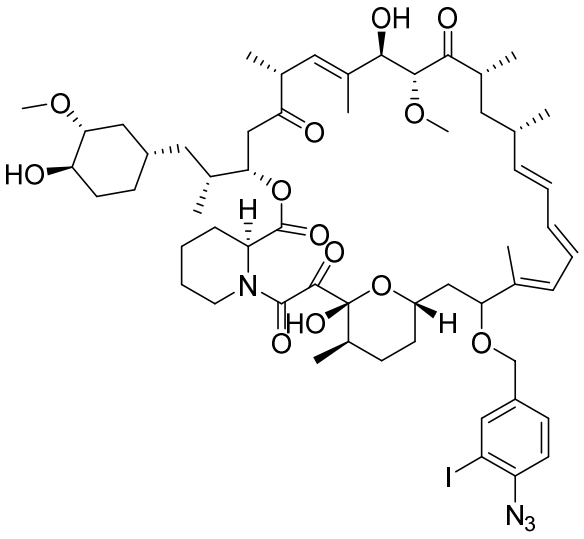
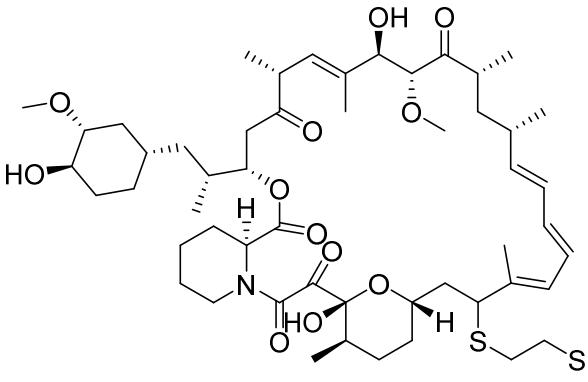
provided said compound is other than:

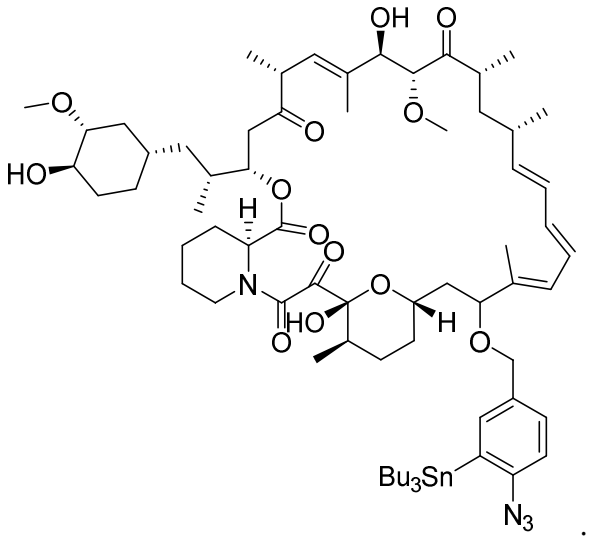
,

,

,

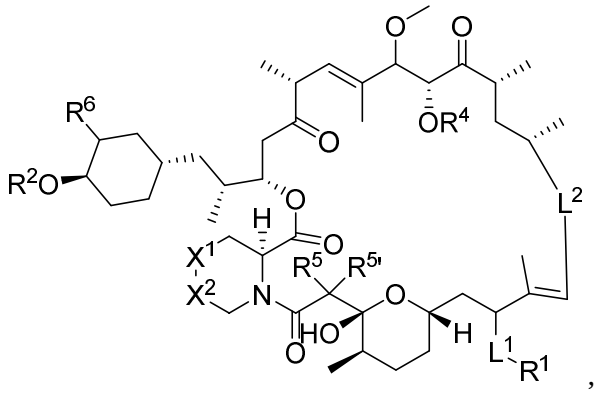

,

,

,

,

,

,

,

,


,

,

,

,

, or



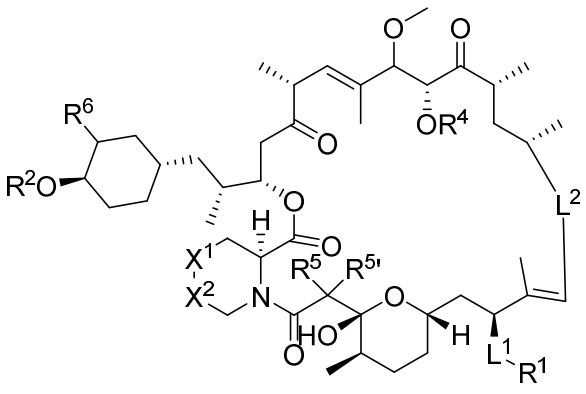
.

2. The compound of claim 1, wherein said compound is selected from any one of the following formulae:



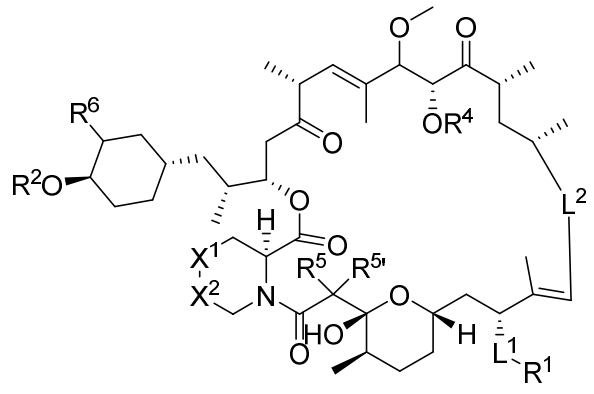
,

I-y-1

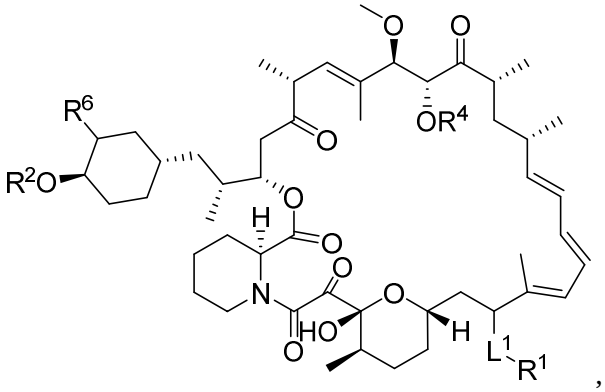


, or

I-y-2

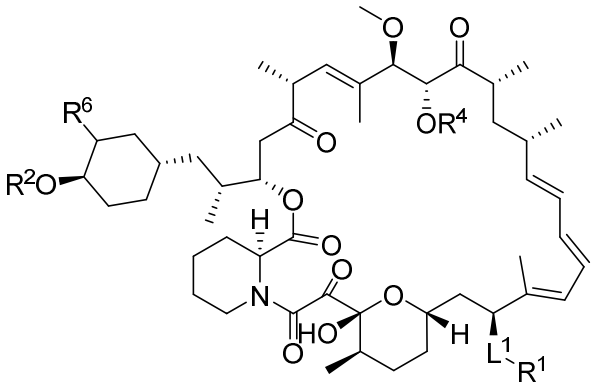


I-y-3



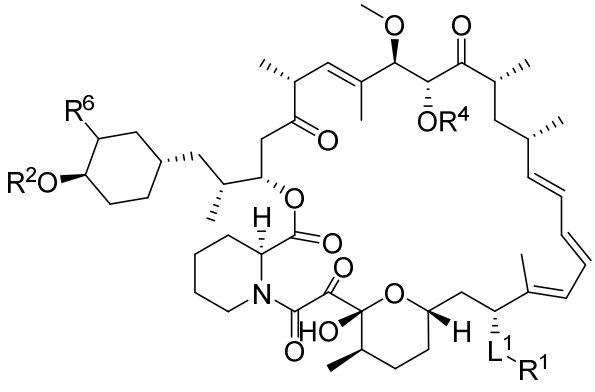
,

I-y-4

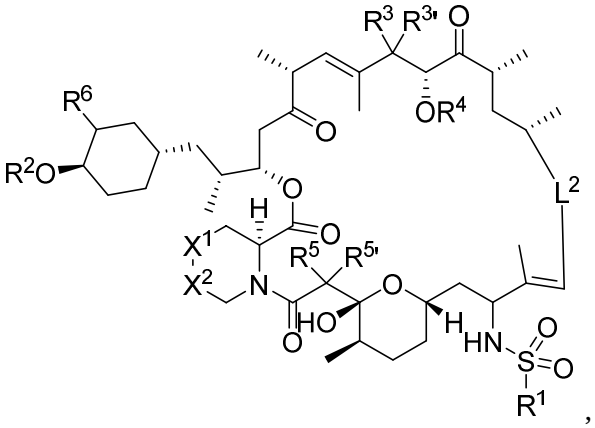


, or

I-y-5

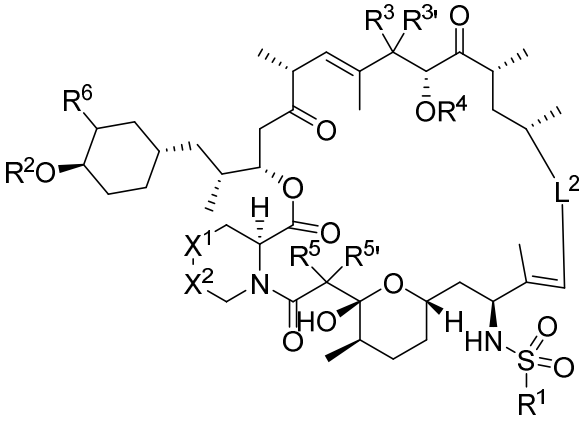


I-y-6



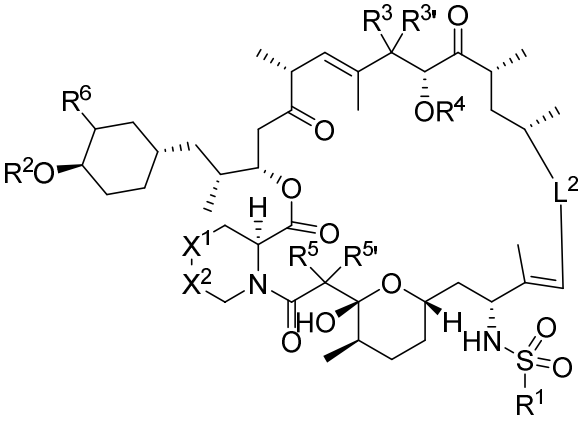
,

I-z-1

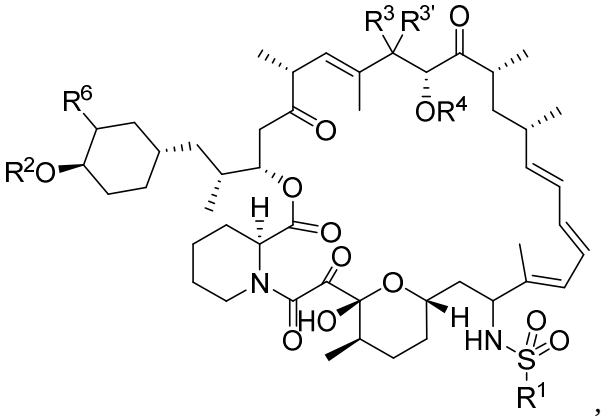


, or

I-z-2

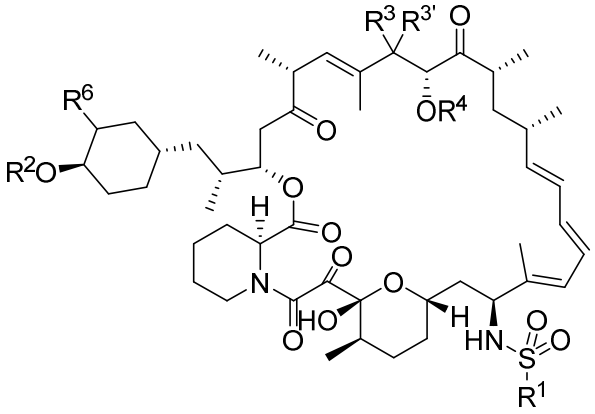


I-z-3



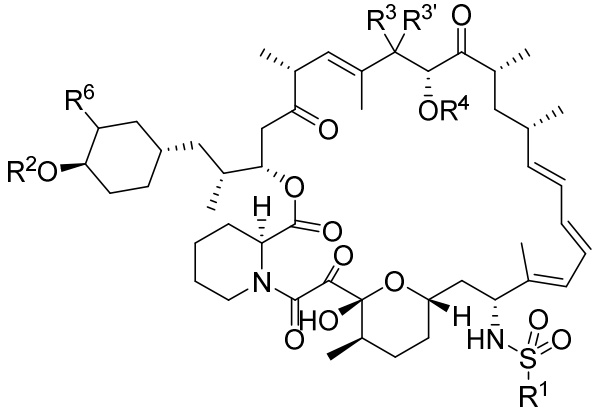
,

I-z-4



, or

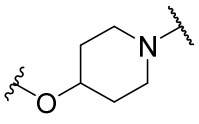
I-z-5



I-z-6

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein L^1 is a C_{1-30} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-10 methylene units of the chain are independently and optionally replaced with $-Cy_1-$, -O-, -S-, $-S(O)_2-$, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-CF_2-$, -P(O)(R)-, $-Si(R)_2-$, -Si(OR(R), or -NR-.

4. The compound of claim 1, wherein L^1 is selected from -O-, -NH-, -O-CH_2-, -O-$(CH_2)_2$-, -O-$(CH_2)_3$-, -O-$(CH_2)_4$-, -O-$(CH_2)_5$-, -O-$(CH_2)_2$-O-, -O-$(CH_2)_2$-O-$(CH_2)_2$-, -NH-CH_2-, -NH-C(O)-, -NH-C(O)O-, -NH-SO_2-, -NH-SO_2-$(CH_2)_2$-, -NH-SO_2-$(CH_2)_2$-O-$(CH_2)_2$-, -O-$(CH_2)_2$-SO_2-$(CH_2)_2$-, -O-$(CH_2)_2$-SO_2-$(CH_2)_2$-SO_2-, -O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-, and 

.

5. The compound of claim 1, wherein L^1 is a covalent bond.

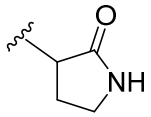
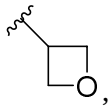
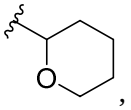
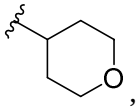
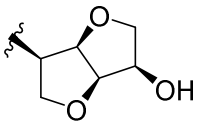
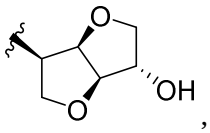
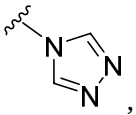
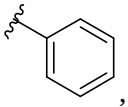
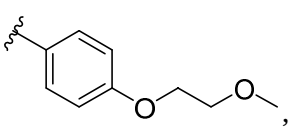
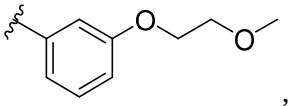
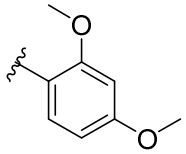
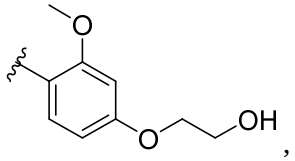
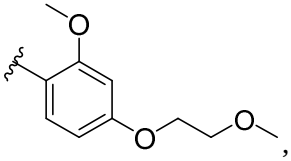
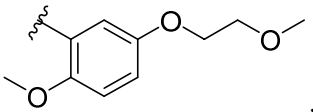
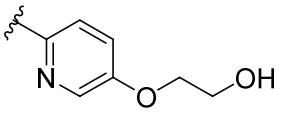
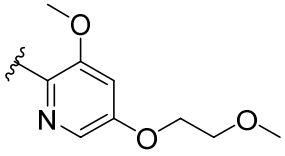
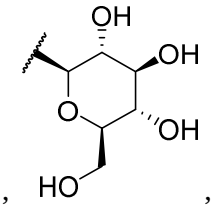
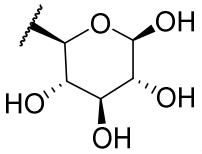
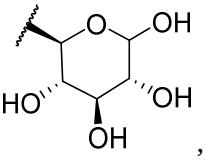
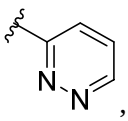
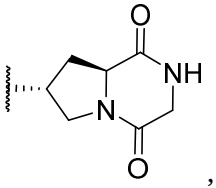
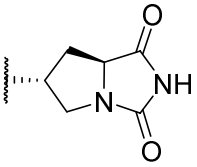
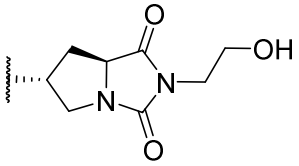
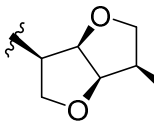
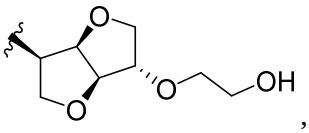
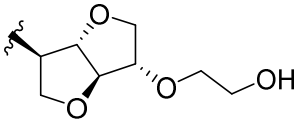
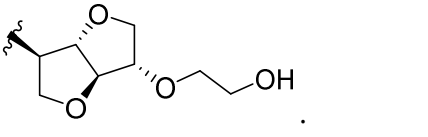
6. The compound of any one of claims 1-5, wherein each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or two R groups on the same nitrogen atom are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen atom to which they are attached, independently selected from nitrogen, oxygen, or sulfur.

7. The compound of any one of claims 1-6, wherein R^1 is selected from hydrogen, halogen, -OR, -CN, -NO_2, or an optionally substituted group selected from a C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfurs, and an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

8. The compound of any one of claims 1-7, wherein R^1 is selected from hydrogen, halogen, -OR, and -NR_2.

9. The compound of any one of claims 1-7, wherein R^1 is an optionally substituted group selected from: a C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms

independently selected from nitrogen, oxygen, or sulfurs, and an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

10. The compound of any one of claims 1-9, wherein R^1 is selected from -OMe, -$(CH_2)_2$-OH, -$(CH_2)_2$-OMe, -SO_2-NH_2, -C(O)NH_2, -C(O)NMe_2, -OC(O)NHMe, -CO_2H, , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

11. The compound according any one of claims 1-10, wherein said compound is selected from those depicted in **Table 1**.

12. A pharmaceutically acceptable composition comprising a compound of any one of claims 1-11, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

13. Use of a compound according to claims 1-11, or a pharmaceutical composition thereof, in the manufacture of a medicament for treating an mTORC-mediated disease, disorder, or condition in a patient in need thereof.

14. The use according to claim 13, further comprising an additional therapeutic agent in combination with said compound.

15. The use according to claim 13, wherein the mTORC-mediated disease, disorder, or condition is selected from diabetic nephropathy, kidney-related complications of type 1 diabetes and type 2 diabetes, autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), kidney diseases associated with cyst formation or cystogenesis, focal segmental glomerulosclerosis (FSGS) and other diseases associated with sclerosis of the kidney, laminopathies, age-related macular degeneration (AMD), diabetic macular edema, diabetic retinopathy, glaucoma, age related retinal disease, immune system senescence, respiratory tract infections, urinary tract infections, heart failure, osteoarthritis, pulmonary arterial hypertension (PAH), and chronic obstructive pulmonary disease (COPD).

16. The use according to claim 13, wherein the mTORC-mediated disease, disorder, or condition is selected from Fragile X syndrome (FXS), amyotrophic lateral sclerosis (ALS), epilepsy, focal cortical dysplasia (FCD), hemimegalencephaly (HME), familial focal epilepsy with variable foci (FFEV), temporal lobe epilepsy (TLE), seizures, neurodegenerative diseases, Down syndrome, Rett syndrome (RTS), and diseases associated with activation or hyperactivation of mTOR signaling in the brain.