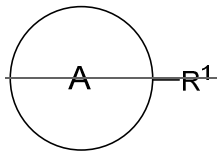
CLAIMS

We claim:

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



I

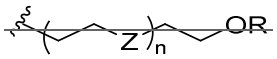
or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a monovalent derivative of rapamycin or an analog thereof;

wherein R^1 is attached thereto at the C7 hydroxyl position of the rapamycin, or analog thereof;

R^1 is an optionally substituted straight or branched saturated or unsaturated monovalent C_{3-30} hydrocarbon chain wherein one or more methylene units of R^1 are optionally and independently replaced by N(R) , N(R)C(O) , C(O)N(R) , N(R)S(O)$_2$, S(O)$_2$N(R) , O , C(O) , OC(O) , C(O)O , S , S(O) , S(O)$_2$, or P(O)(R)$_2$; or a 6-18 membered saturated or partially unsaturated heterocyclic ring having 1-6 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

R^1 is selected from Formula **P-0**:



P-0

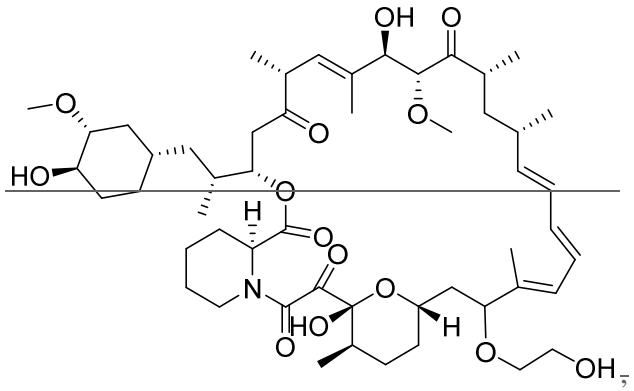
wherein:

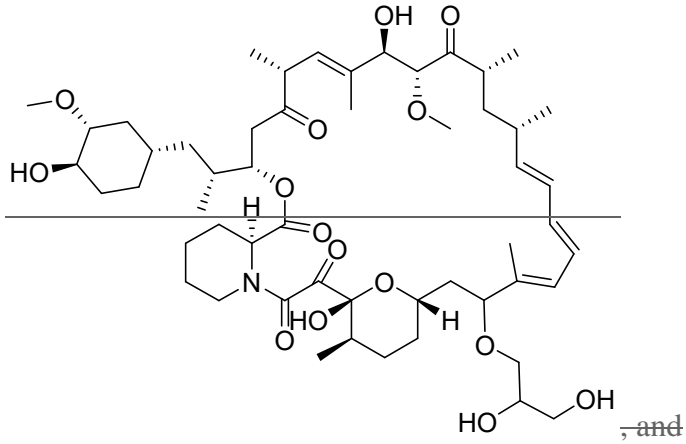
indicates the attachment point to Ring A;

each Z is independently -O-, -S-, -NR-, or -SO$_2$-;

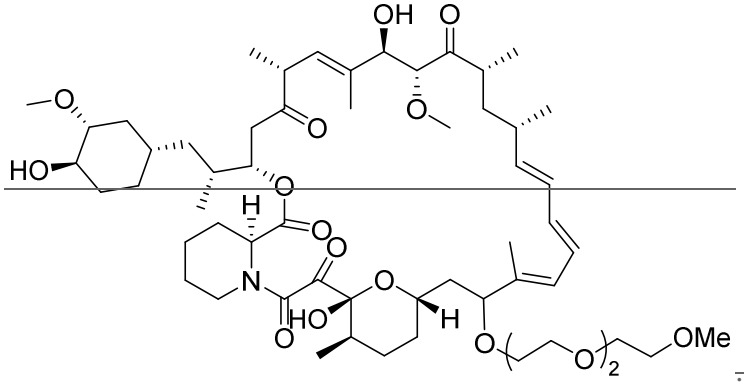
n is from about 2 to about 300; and

each R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, provided that said compound is other than:





, and



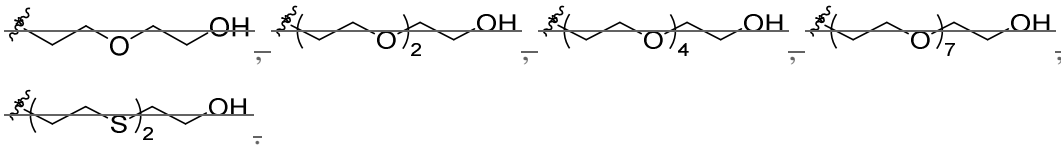
.

2. The compound of claim 1, wherein Ring A is selected from rapamycin and everolimus.

3. The compound of either of claims 1 or 2, wherein R^1 is an optionally substituted straight or branched saturated or unsaturated monovalent C_{3-30} hydrocarbon chain, wherein one or more methylene units of R^1 are optionally and independently replaced by $-N(R)-$, $-N(R)C(O)-$, $-C(O)N(R)-$, $-N(R)S(O)_2-$, $-S(O)_2N(R)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-P(O)(R)_2-$.

4. The compound of any of claims 1 to 3, wherein R^1 is an optionally substituted straight or branched saturated or unsaturated monovalent C_{3-30} hydrocarbon chain, wherein one or more methylene units of R^1 are optionally and independently replaced by –O– or –S–.

5. The compound of any of claims 1 to 4, wherein R^1 is selected from

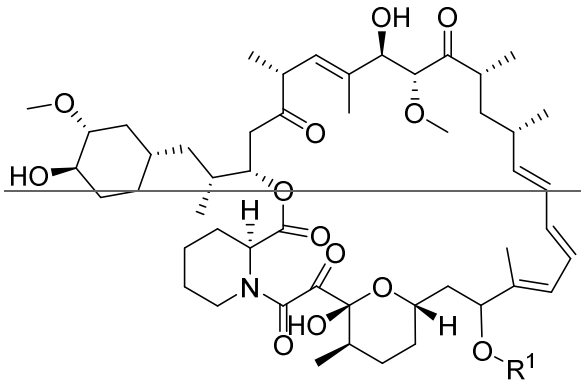


, and

.

6. The compound according to either of claim 1 or claim 2, wherein R^1 is a 6–18 membered saturated or partially unsaturated heterocyclic ring having 1–6 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

7. A compound of Formula **II**:

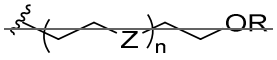


II

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is an optionally substituted straight or branched saturated or unsaturated monovalent C_{3-30} hydrocarbon chain wherein one or more methylene units of R^1 are optionally and independently replaced by –N(R)–, –N(R)C(O)–, –C(O)N(R)–, –N(R)S(O)$_2$–, –S(O)$_2$N(R)–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –S–, –S(O)–, –S(O)$_2$–, or –P(O)(R)$_2$–; or a 6–18 membered saturated or partially unsaturated heterocyclic ring having 1–6 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

R^1 is selected from Formula **P-0**:



P-0

wherein:

~~$\sim\!\!\sim$ indicates the attachment point to the C-7 hydroxyl position;~~

~~each Z is independently -O-, -S-, -NR-, or -SO_2-;~~

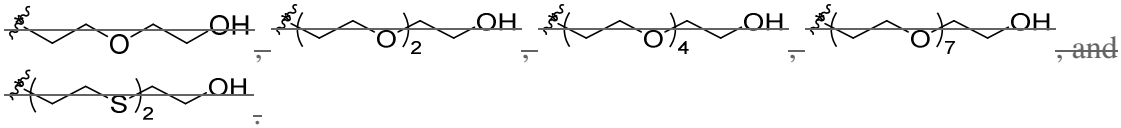
~~n is from about 2 to about 300; and~~

~~each R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group.~~

~~8. The compound of claim 7, wherein R^1 is an optionally substituted straight or branched saturated or unsaturated monovalent C_{3-30} hydrocarbon chain, wherein one or more methylene units of R^1 are optionally and independently replaced by -N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)-, -S(O)$_2$-, or -P(O)(R)$_2$-.~~

~~9. The compound of either of claims 7 or 8, wherein R^1 is an optionally substituted straight or branched saturated or unsaturated monovalent C_{3-30} hydrocarbon chain, wherein one or more methylene units of R^1 are optionally and independently replaced by -O- or -S-.~~

~~10. The compound of any of claims 7 to 9, wherein R^1 is selected from~~

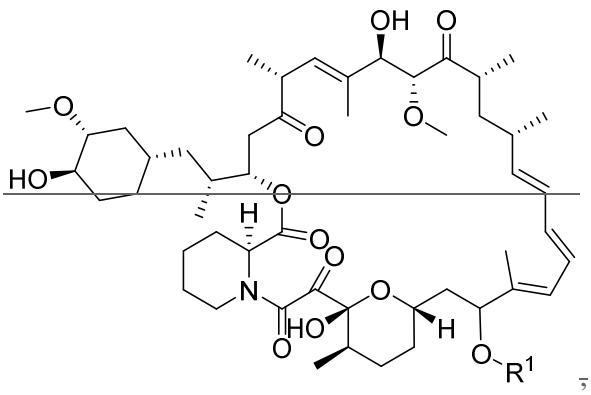


~~, and~~

~~.~~

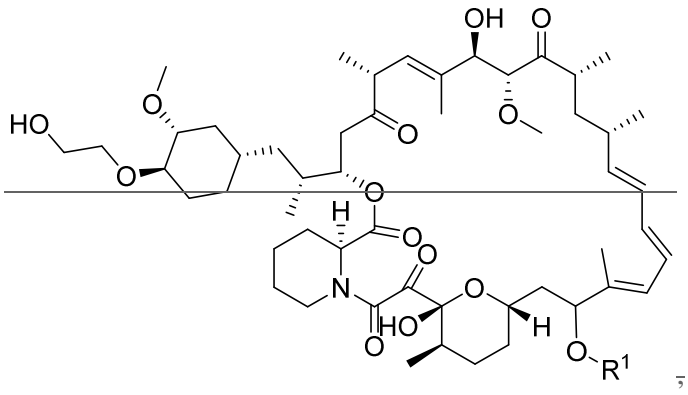
~~11. The compound according to claim 7, wherein R^1 is a 6-18 membered saturated or partially unsaturated heterocyclic ring having 1-6 heteroatoms independently selected from nitrogen, oxygen, or sulfur.~~

~~12. The compound according to claim 1, wherein said compound is selected from any one of Formulae **II, III, IV, V, VI**, **VII**, and **VIII**:~~

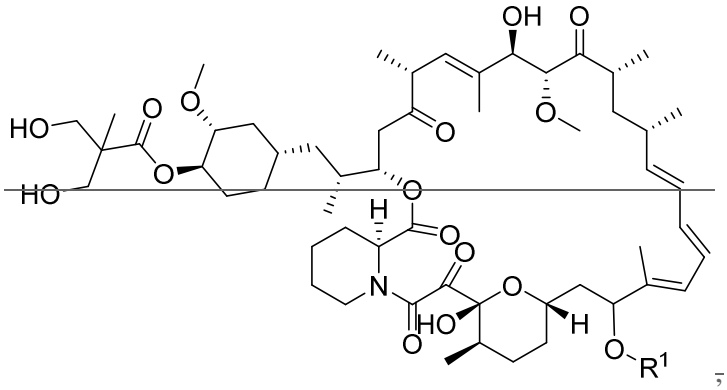


~~,~~

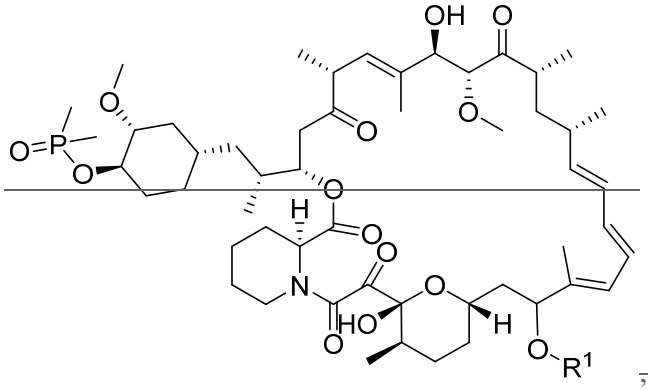
~~II~~



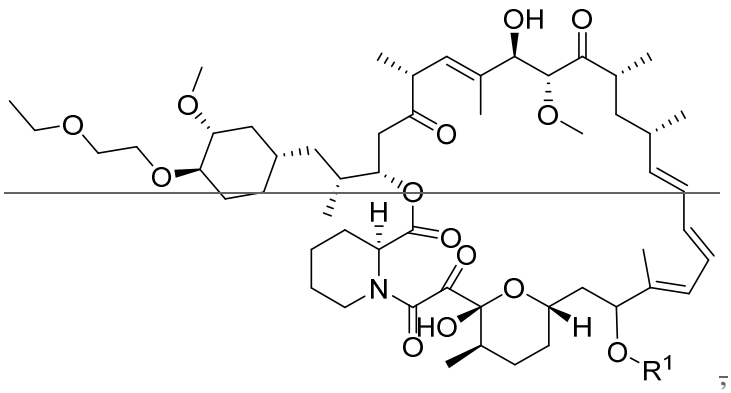
~~III~~



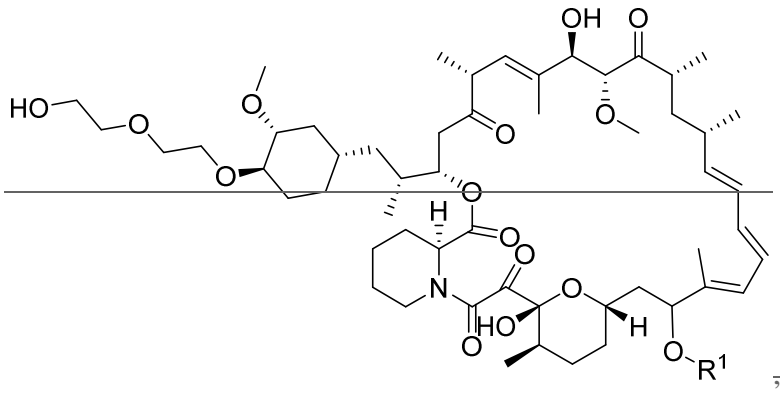
~~IV~~



~~V~~

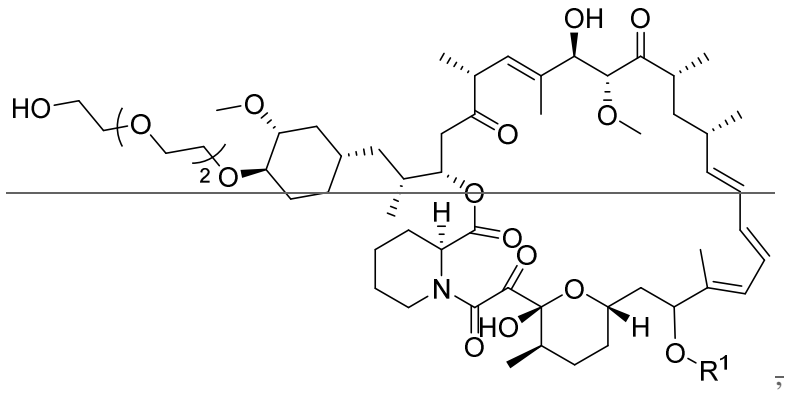


~~VI~~



~~, and~~

~~VII~~

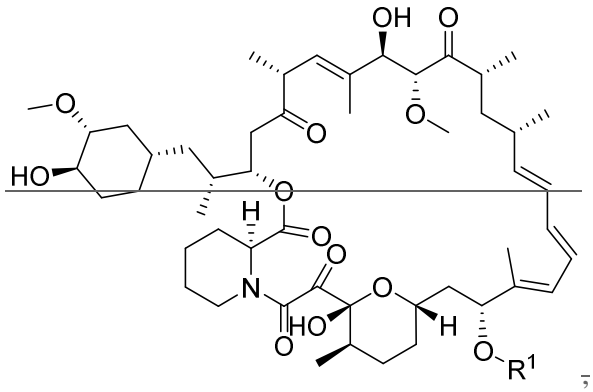


~~,~~

~~VIII~~

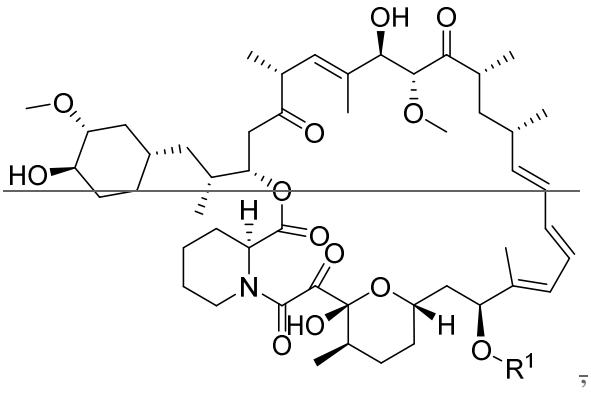
~~or a pharmaceutically acceptable salt thereof.~~

~~13. The compound of claim 1 or claim 12, wherein said compound is selected from any one of Formulae **II-a**, **II-b**, **III-a**, and **III-b**:~~

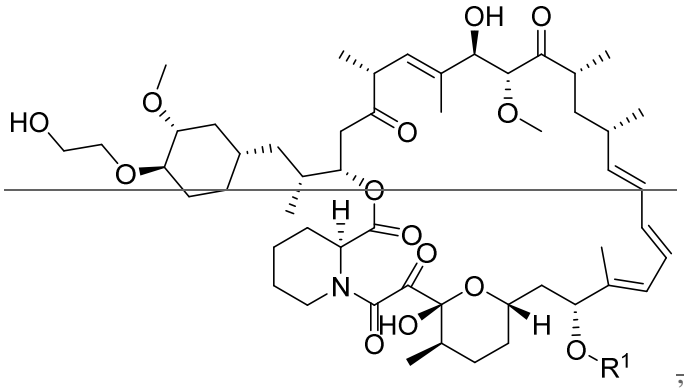


~~,~~

~~**II-a**~~

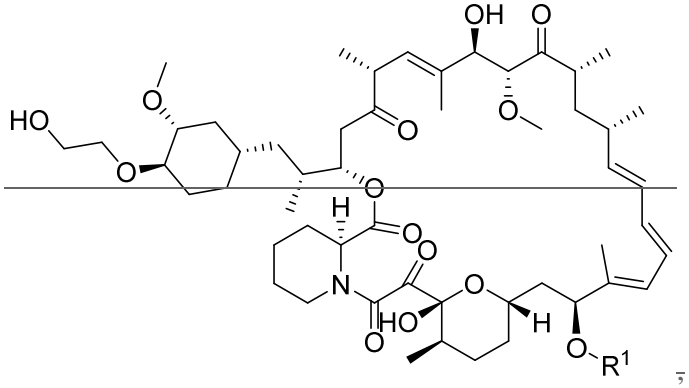


~~II-b~~



~~, and~~

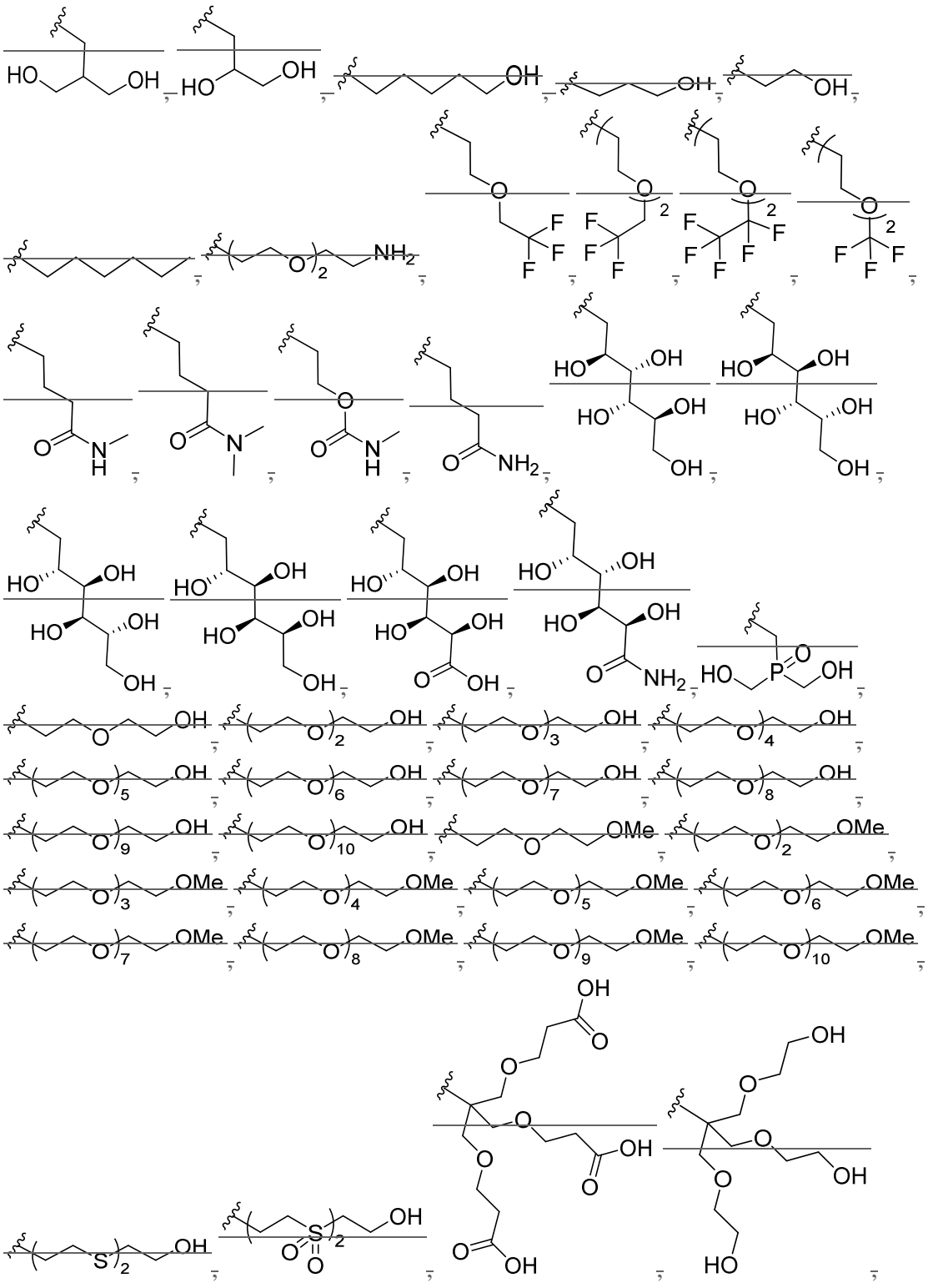
~~III-a~~

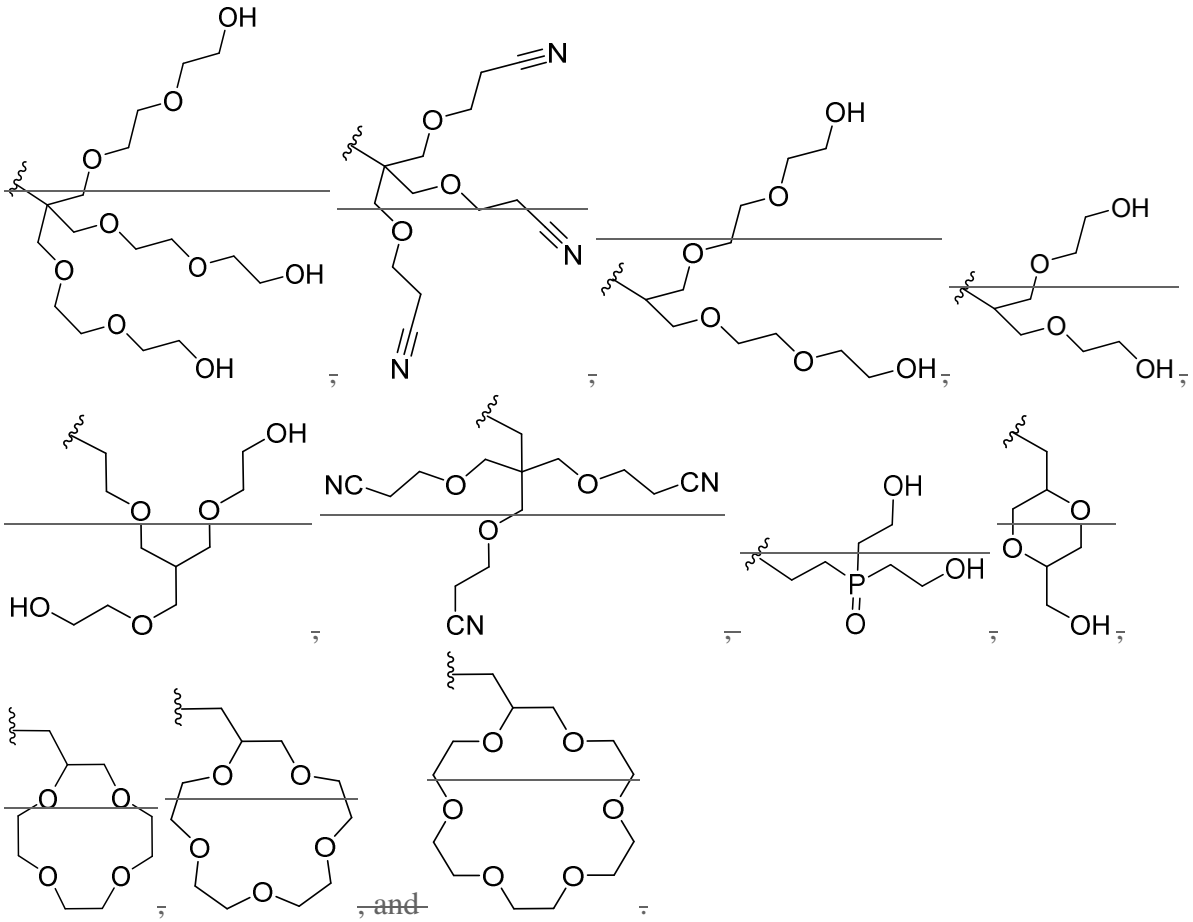


~~III-b~~

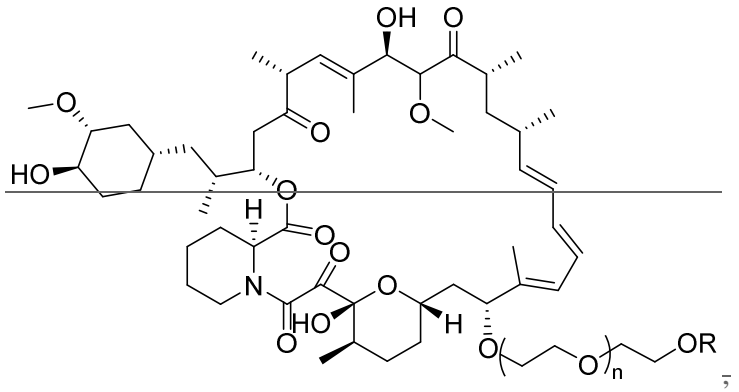
~~or a pharmaceutically acceptable salt thereof.~~

~~14. The compound of any one of claims 1, 7, 12, or 13, wherein R^1 is selected from:~~

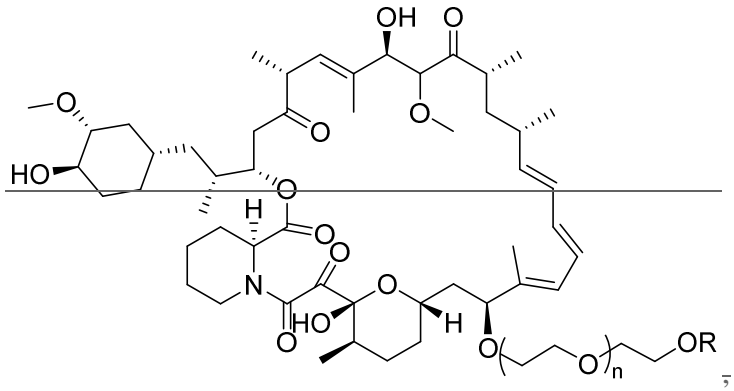




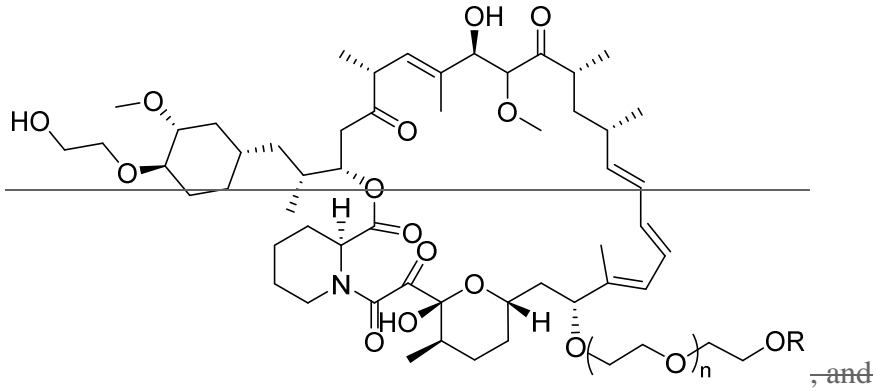
~~15. The compound according to claim 1 or claim 12, wherein said compound is selected from any of Formulae **XII-a**, **XII-b**, **XIII-a**, and **XIII-b**:~~



~~**XII-a**~~

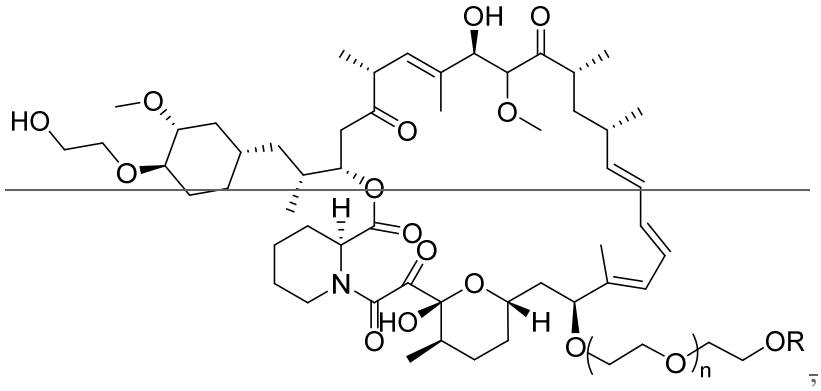


~~XII-b~~



~~, and~~

~~XIII-a~~



~~XIII-b~~

~~or a pharmaceutically acceptable salt thereof.~~

~~16. The compound according to claim 1, wherein said compound is selected from those depicted in **Table 1**.~~

~~17. A pharmaceutically acceptable composition comprising a compound of any of claims 1 through 16, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.~~

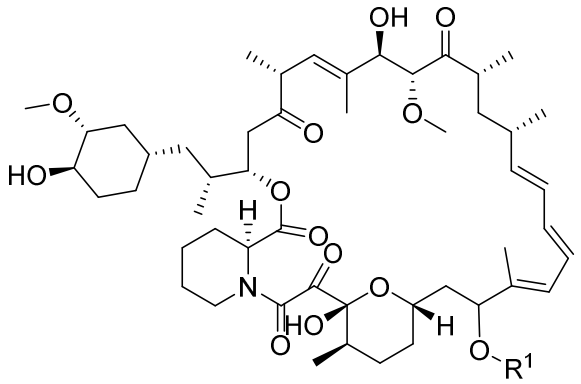
~~18. A method of treating an mTORC-mediated disease, disorder, or condition in a patient in need thereof, comprising administering to said patient the compound of any of claims 1 to 16, or a pharmaceutical composition thereof.~~

~~19. The method according to claim 18, 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).~~

~~20. The method according to any one of claims 18 or 19, further comprising administering an additional therapeutic agent in combination with said compound.~~

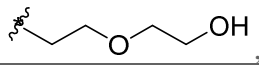
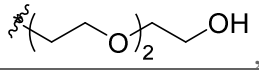
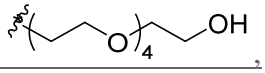
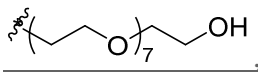
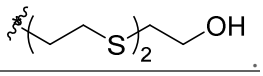
~~21. The use of the compound or composition of any one of claims 1 to 16 for the manufacture of a medicament for the treatment of an mTORC-mediated disorder in a patient in need thereof.~~

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

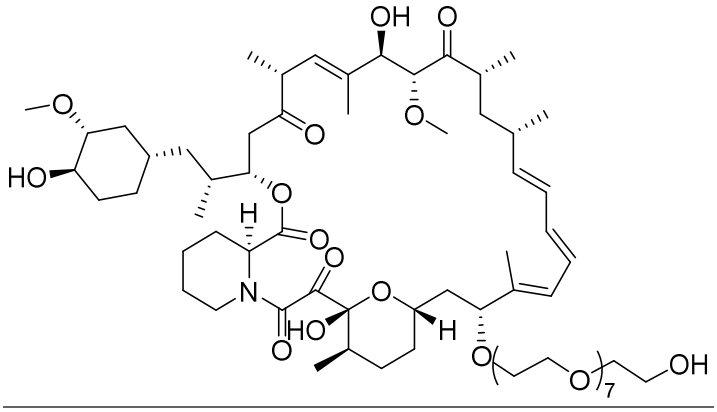


II

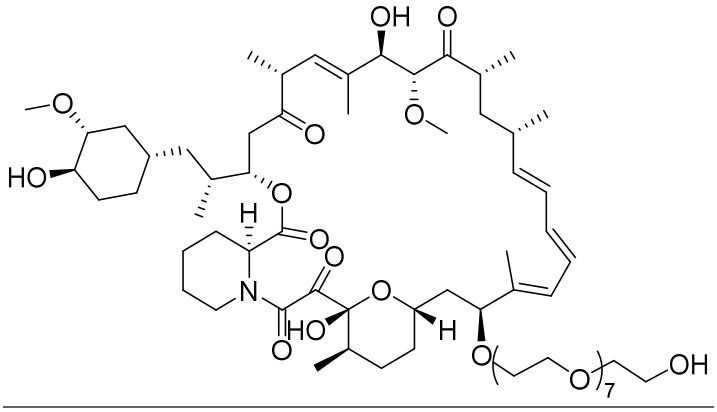
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from , , , , and .

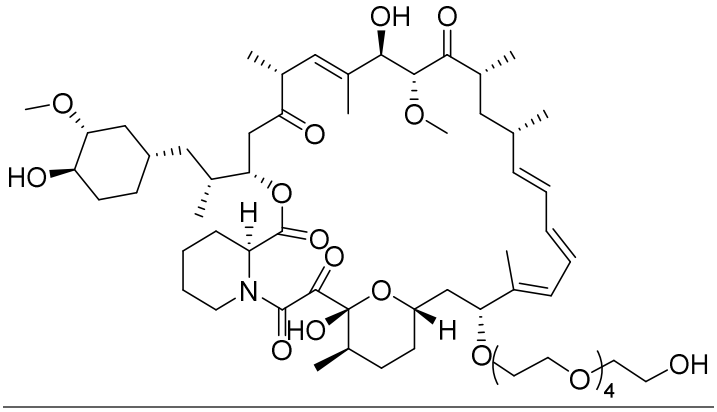
2. The compound according to claim 1, wherein said compound is selected from:



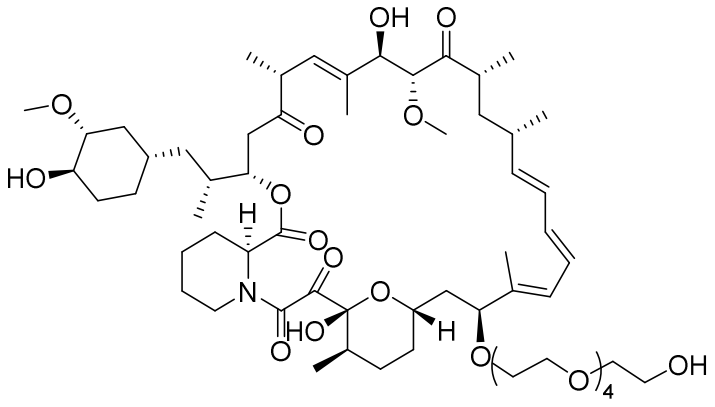
I-8



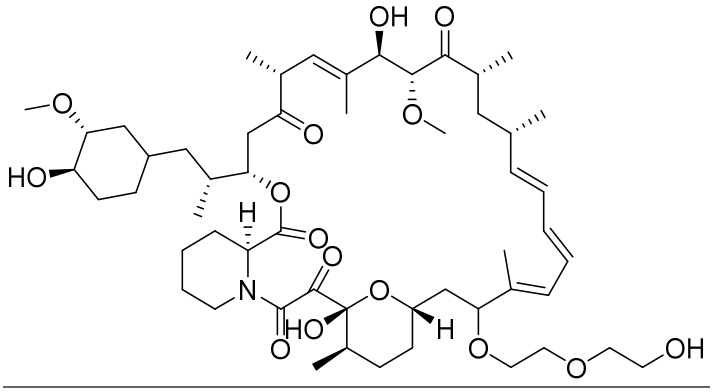
I-9



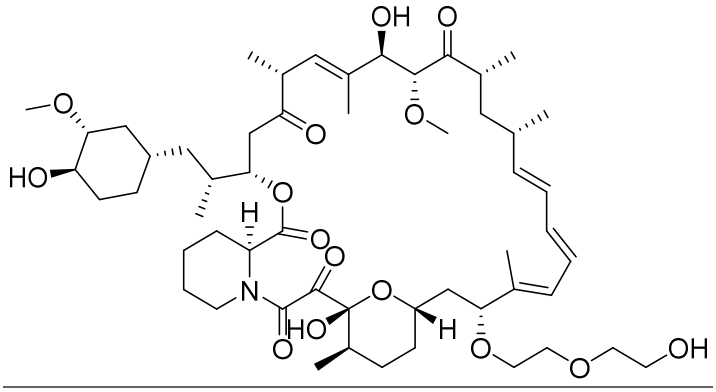
I-13



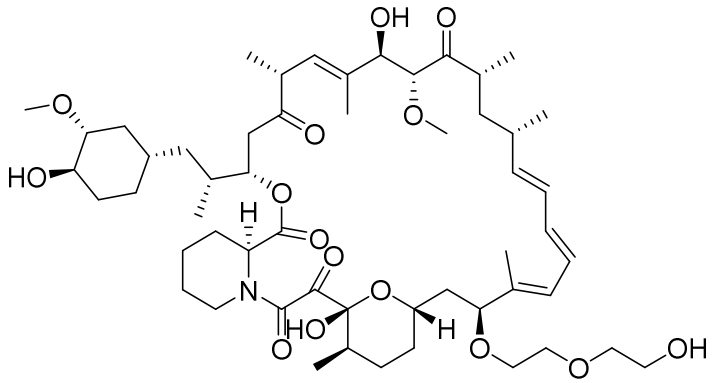
I-14



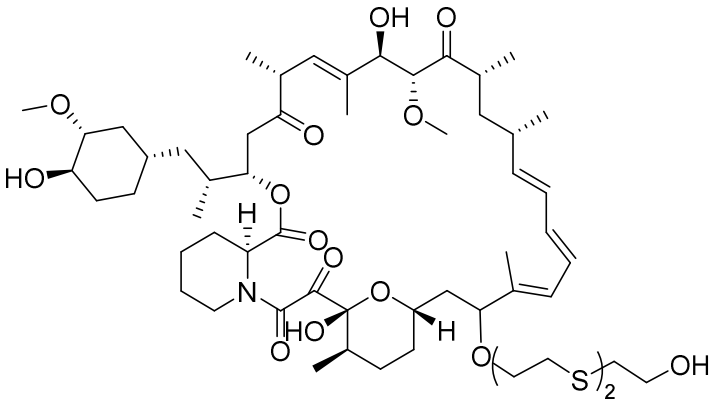
I-18



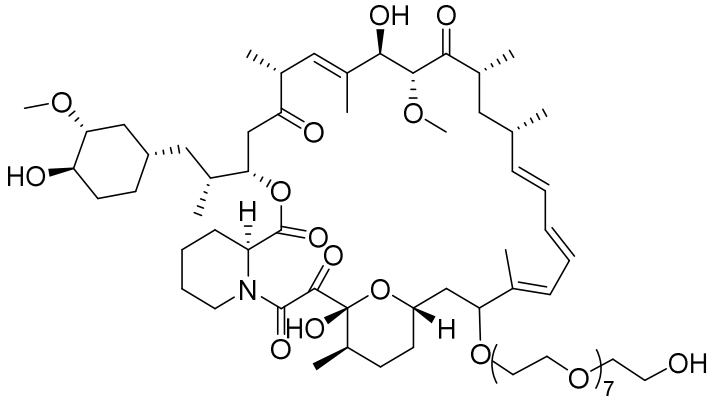
I-19



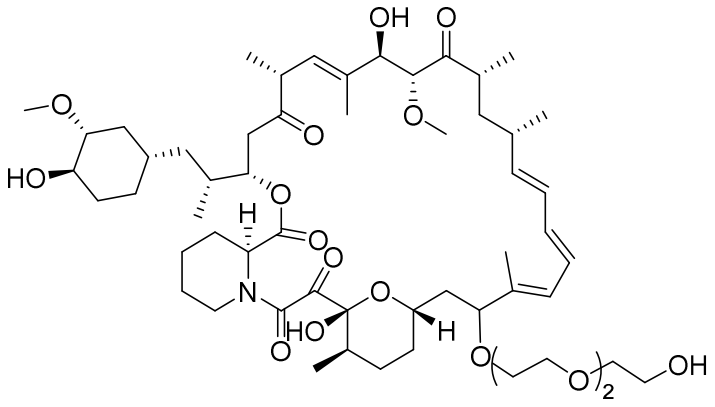
I-20



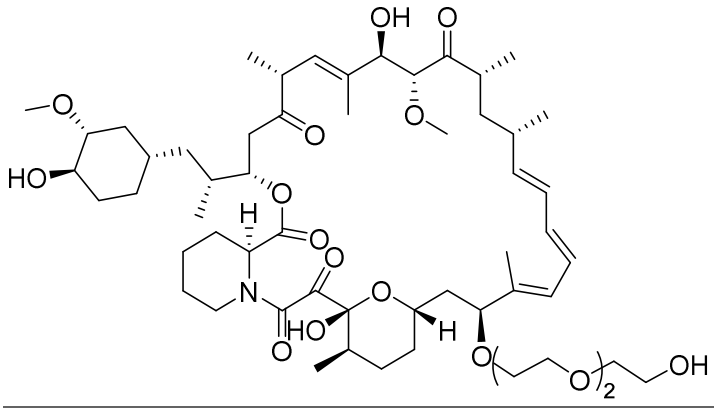
I-21



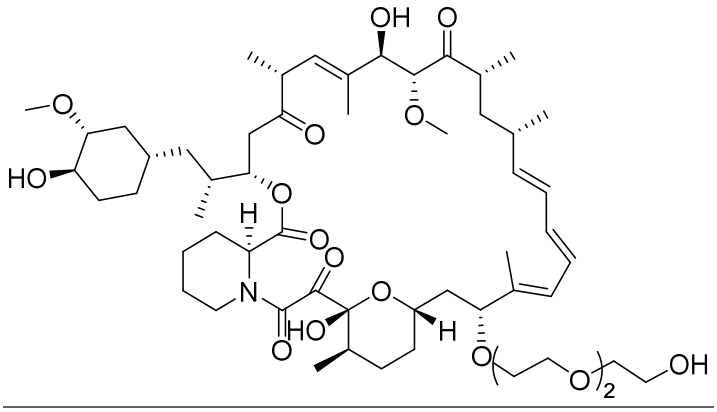
I-24



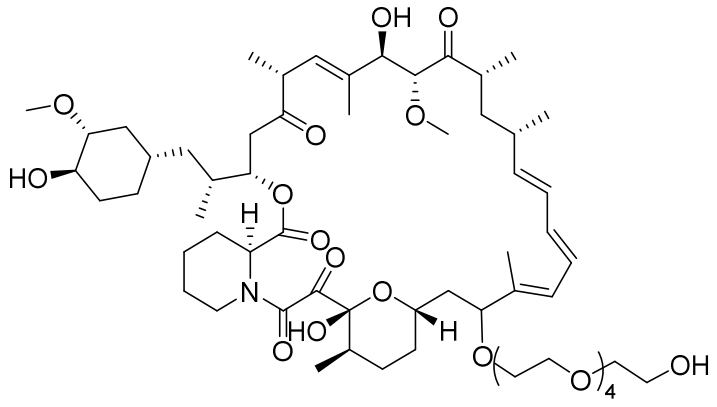
I-28



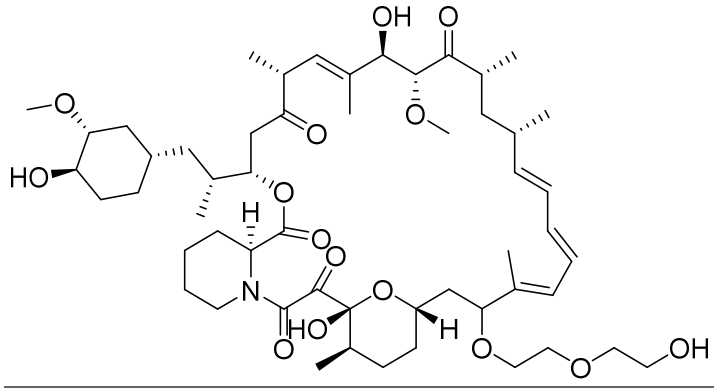
I-29



I-30



I-35



I-37

or pharmaceutically acceptable salt thereof.

3. A pharmaceutically acceptable composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

4. A pharmaceutically acceptable composition comprising a compound of claim 2, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.