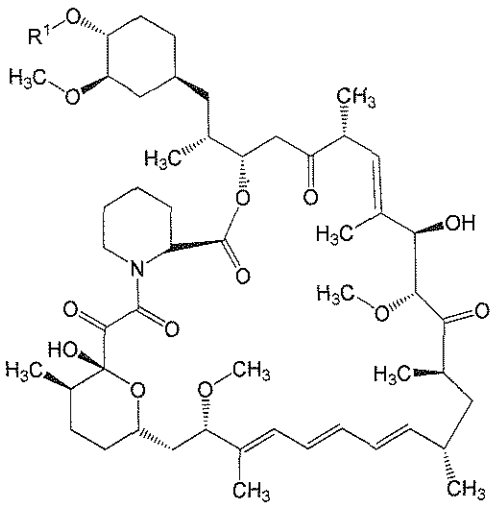
autoimmune diseases, and conditions characterized by excessive cell proliferation. The chemical structure of BA9 consists of a 31-membered triene macrolide lactone that preserves the core rapamycin ring structure and differs only in the addition of a side chain at position 40 in which the hydroxyl group of rapamycin has been alkylated with an ethoxyethyl group.

[0005] The chemical structure of BA9 compared to sirolimus and other sirolimus derivatives is provided in Figure 1. The structure consists of the rapamycin 31-membered macrolide triene lactone ring with ethoxyethylation at position 40. BA9, like sirolimus, binds to the intracellular immunophilin protein FKBP12. It is believed that the resulting macrolide/FKBP-12 complex then binds, in a manner similar to sirolimus, to mTOR, a protein critical for cell cycle progression. Inactivation of mTOR results in suppression of several specific signal transduction pathways and arrest of the cell cycle at the G1 to S phase.

[0006] Given the therapeutic value of BA9 and other rapamycin derivatives, improved processes for preparation of this family of active agents is needed. The present invention addresses this and other needs.

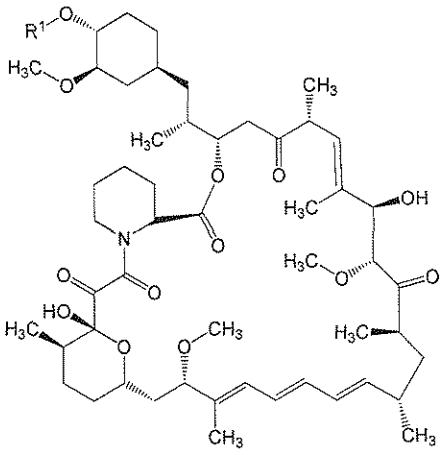
BRIEF SUMMARY

[0007] The present disclosure provides a method for obtaining a compound having the structure of Formula I:



(I).

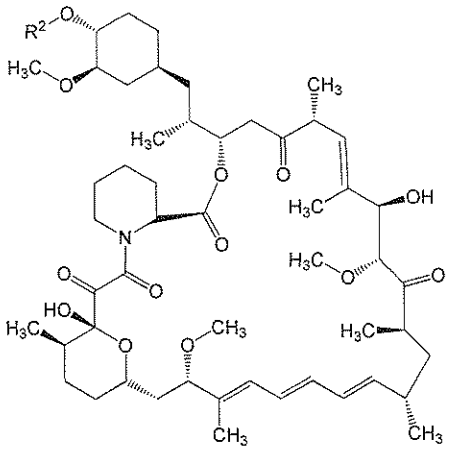
[0007a] In one aspect of the present disclosure, there is provided a method for obtaining a compound having the structure of Formula I



(I),

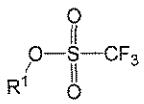
the method comprising:

a) combining in a reaction mixture an organic solvent, an organic base compound having a nitrogen heteroatom, a compound having the structure of Formula II



(II), and

a compound having the structure of Formula III



(III);

b) maintaining the reaction mixture at a temperature of from 25 °C to 55 °C; and

c) separating from the reaction mixture a compound having the structure of Formula I;

wherein

R^1 is $(CH_2)_e$–O– $(CH_2)_f$–H;

e is an integer selected from 1-5;

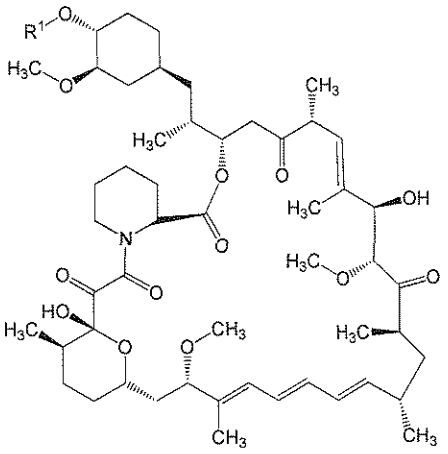
f is an integer selected from 1-5; and

R^2 is hydrogen;

thereby obtaining a compound having the structure of Formula I.

WHAT IS CLAIMED IS:

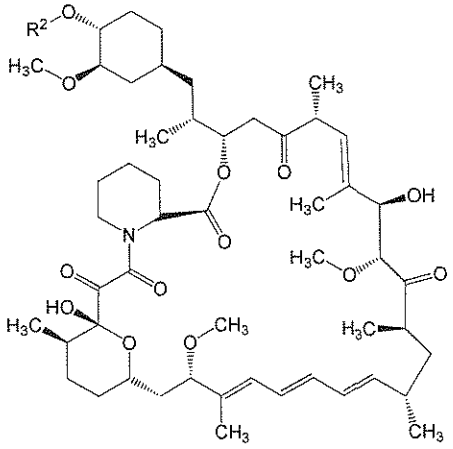
1. A method for obtaining a compound having the structure of Formula I



(I),

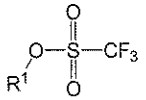
the method comprising:

a) combining in a reaction mixture an organic solvent, an organic base compound having a nitrogen heteroatom, a compound having the structure of Formula II



(II), and

a compound having the structure of Formula III



(III);

b) maintaining the reaction mixture at a temperature of from 25 °C to 55 °C; and

c) separating from the reaction mixture a compound having the structure of Formula I;

wherein

R^1 is $(CH_2)_e$–O– $(CH_2)_f$–H;

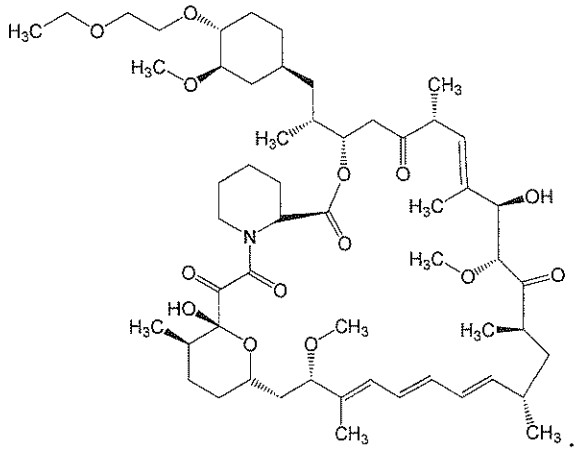
e is an integer selected from 1-5;

f is an integer selected from 1-5; and

R^2 is hydrogen;

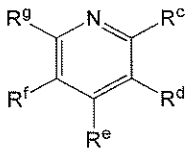
thereby obtaining a compound having the structure of Formula I.

2. The method of claim 1, wherein the compound having the structure of Formula I is



3. The method of claim 1, wherein R^1 is CH_2–CH_2–O–CH_2–CH_3.

4. The method of claim 1, wherein the organic base compound having a nitrogen heteroatom has the structure of Formula IV



(IV);

wherein:

R^c, R^d, R^e, R^f, and R^g are each independently selected from the group consisting of H, $C_{1\text{-}5}$alkyl, OH, and NH_2.

5. The method of claim 1, wherein the organic base compound having a nitrogen heteroatom is selected from 2,6-lutidine and *N,N*-diisopropylethylamine.

6. The method of claim 1, wherein the organic base compound having a nitrogen heteroatom is 2,6-lutidine.

7. The method of claim 1, wherein the maintaining in part (b) is for 2-10 hours.

8. The method of claim 7, wherein the maintained temperature in part (b) is from 25 to 40 °C.

9. The method of claim 1 wherein the organic solvent is toluene or methylene chloride.

10. The method of claim 1, wherein the molar ratio of the compound having the structure of Formula III to the compound having the structure of Formula II is from 30 to 1 to 60 to 1.

11. The method of claim 1, wherein the molar ratio of the organic base compound having a nitrogen heteroatom to the compound having the structure of Formula II is from 80 to 1 to 120 to 1.

12. The method of claim 11, wherein the ratio is 104 to 1.

13. The method of claim 1, wherein the organic base compound having a nitrogen heteroatom is added in two separate portions.

14. The method of claim 1, wherein separating the compound having the structure of Formula I comprises using chromatography.

15. The method of claim 14, wherein the chromatography is selected from the group consisting of silica gel column chromatography, high-pressure liquid chromatography, and thin layer chromatography.

16. The method of claim 15, wherein the chromatography is silica gel column chromatography, and wherein the chromatography is conducted using a mobile phase comprising one or more solvents selected from the group consisting of ethyl acetate, hexane, and heptane.

17. The method of claim 1, further comprising solidifying the compound having the structure of Formula I.

18. The method of claim 17, wherein solidifying the compound having the structure of Formula I comprises

a) solubilizing the compound having the structure of Formula I in methanol; and

b) precipitating the compound having the structure of Formula I from water;