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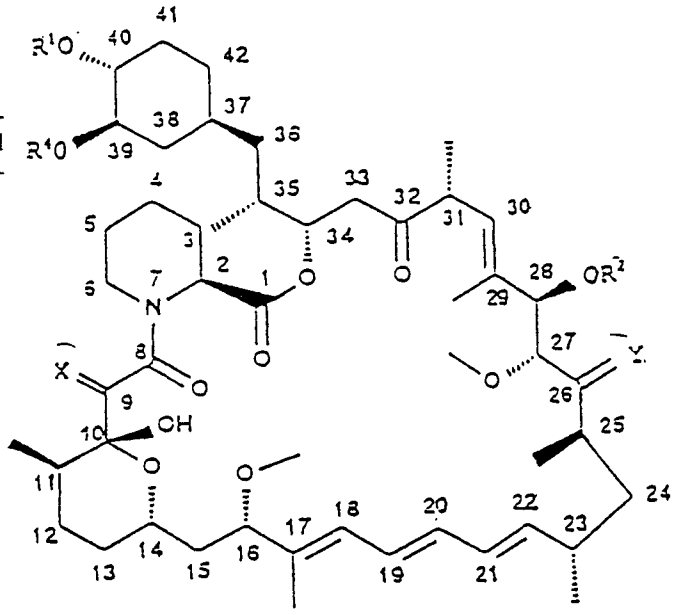
(54) Title: O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNOSUPPRESSANTS

(57) Abstract

Novel O-alkylated derivatives of rapamycin of formula (I), especially 40-O-alkylated derivatives, are found to have pharmaceutical utility, particularly as immunosuppressants.



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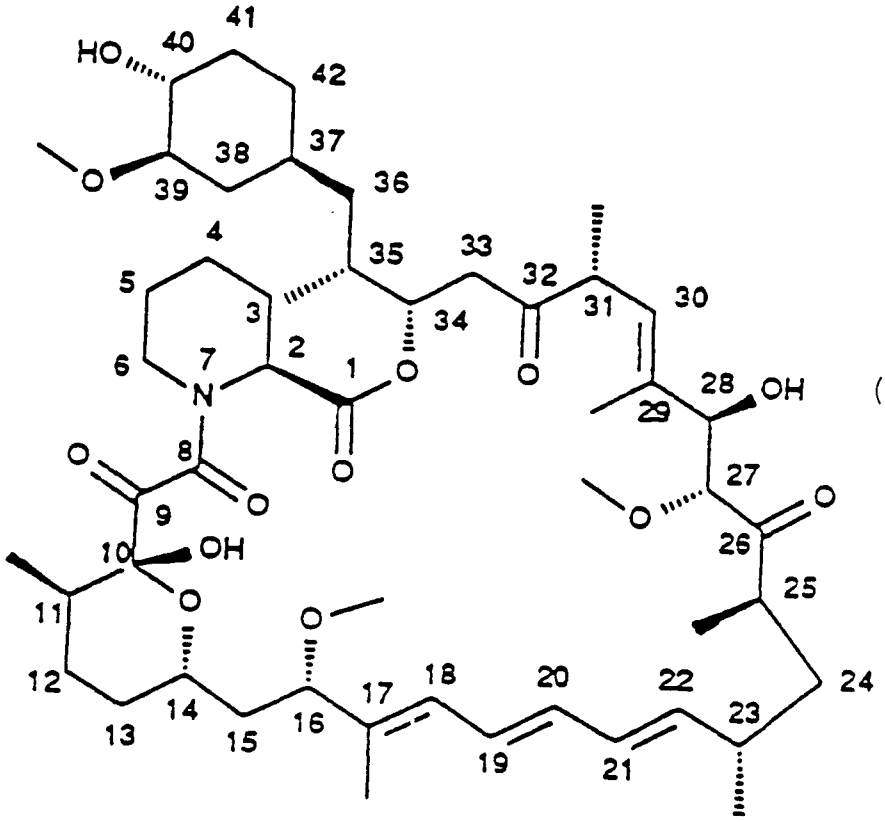
O-ALKYLATED RAPAMYCIN DERIVATIVES AND THEIR USE, PARTICULARLY AS IMMUNO-SUPPRESSANTS

This invention comprises novel alkylated derivatives of rapamycin having pharmaceutical utility, especially as immunosuppressants.

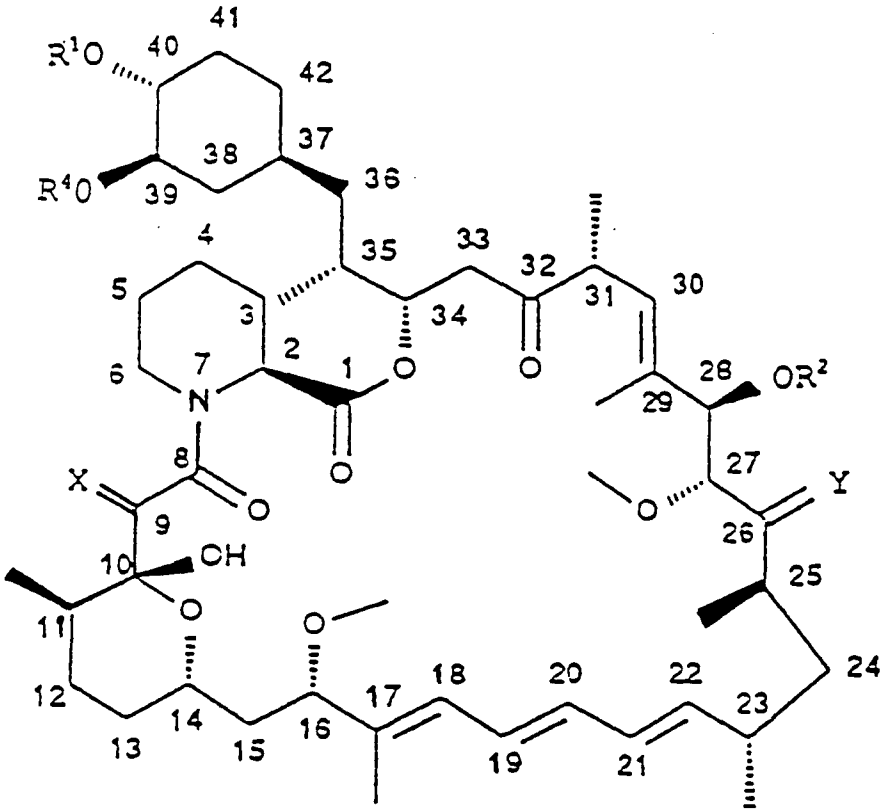
Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus, having the structure depicted in Formula A:



See, e.g., McAlpine, J.B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S.L., et al., J. Am. Chem. Soc. (1991) 113: 7433; US Patent No. 3 929 992. Rapamycin is an extremely

potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability as well as its high toxicity. Moreover, rapamycin is highly insoluble, making it difficult to formulate stable galenic compositions.

It has now surprisingly been discovered that certain novel derivatives of rapamycin (the Novel Compounds) have an improved pharmacologic profile over rapamycin, exhibit greater stability and bioavailability, and allow for greater ease in producing galenic formulations. The Novel Compounds are alkylated derivatives of rapamycin having the structure of Formula I:



(I)

wherein

X is (H,H) or O;

Y is (H,OH) or O;

R^1 and R^2 are independently selected from

H, alkyl, thioalkyl, arylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylarylalkyl, dihydroxyalkylarylalkyl, alkoxyalkyl, acyloxyalkyl, aminoalkyl, alkylaminoalkyl, alkoxycarbonylaminoalkyl, acylaminoalkyl, arylsulfonamidoalkyl, allyl, dihydroxyalkylallyl, dioxolanylallyl, carbalkoxyalkyl, and $(R^3)_3Si$ where each R^3 is independently selected from H, methyl, ethyl, isopropyl, t-butyl, and phenyl; wherein "alk-" or "alkyl" refers to C_{1-6} alkyl, branched or linear preferably C_{1-3} alkyl, in which the carbon chain may be optionally interrupted by an ether (-O-) linkage; and

R^4 is methyl, or R^4 and R^1 together form C_{2-6} alkylene;

provided that R^1 and R^2 are not both H; and
provided that where R^1 is $(R^3)_3Si$ or carbalkoxyalkyl, X and Y are not both O.

Preferred Novel Compounds include the following:

1. 40-O-Benzyl-rapamycin
2. 40-O-(4'-Hydroxymethyl)benzyl-rapamycin
3. 40-O-[4'-(1,2-Dihydroxyethyl)]benzyl-rapamycin
4. 40-O-Allyl-rapamycin
5. 40-O-[3'-(2,2-Dimethyl-1,3-dioxolan-4(S)-yl)-prop-2'-en-1'-yl]-rapamycin
6. (2'E, 4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin
7. 40-O-(2-Hydroxy)ethoxycarbonylmethyl-rapamycin
8. 40-O-(2-Hydroxy)ethyl-rapamycin

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