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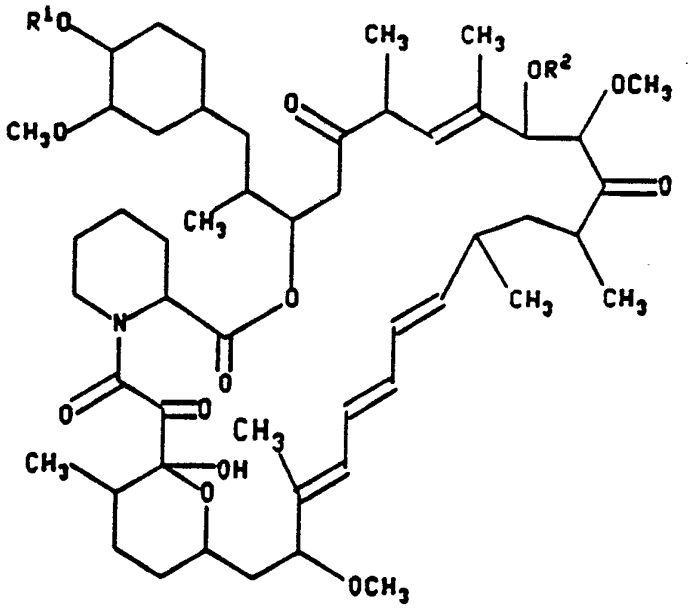

(I)

(57) Abstract

The use of rapamycin prodrugs of formula (I) as immunosuppressant agents, intermediates formed in the preparation of its prodrugs as well as the prodrugs themselves.

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USE OF RAPAMYCIN PRODRUGS AS IMMUNOSUPPRESSANT AGENTS

Background of the Invention

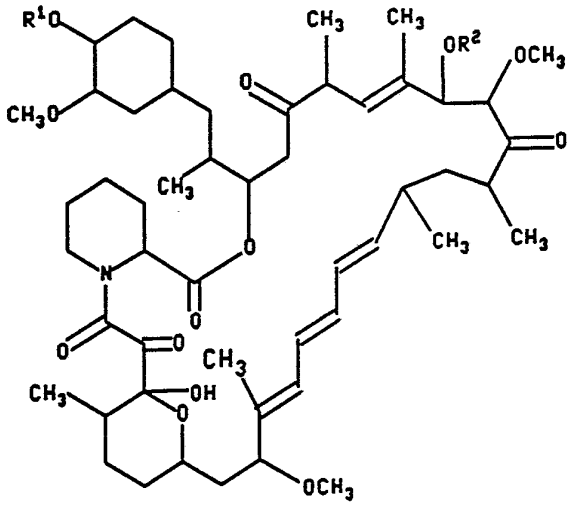
This invention relates to the use of rapamycin prodrugs as immunosuppressant agents, e.g. for use in a human host in the treatment of autoimmune diseases and/or prevention of organ transplant rejections, intermediates formed in the preparation of the prodrugs as well as the prodrugs themselves.

In 1983, the United States Food and Drug Administration licensed cyclosporin A, an anti-rejection drug that revolutionized the field of organ transplant surgery. The drug acts by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. Although cyclosporin A is effective in fighting transplantation rejection, it suffers drawbacks in causing kidney failure, liver damage, and ulcers which in many cases can be very severe. Newer, safer drugs exhibiting less side effects are constantly being searched for.

Rapamycin has been found to be useful as an antifungal agent, United States Patent 3,929,992, as well as capable of inhibition of the immune response, Martel, et al., Can. J. Physiol. Pharmacol. 55, 48-51 (1977).

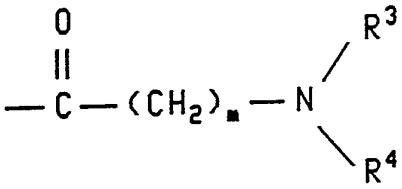
Summary of the Invention

The present invention relates to a method for suppressing the immune system, for example, in treating autoimmune disease or preventing or ameliorating organ or tissue transplant rejection comprising administering to a mammal in need of such treatment an effective immunosuppressive amount of a compound of the formula



I

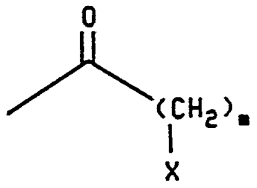
wherein R^1 and R^2 are independently selected from hydrogen, and a group of the formula



II

wherein m is 1-6, R^3 and R^4 are each hydrogen; branch or straight C_1 to C_8 alkyl; cyclic C_3 to C_8 alkyl; phenyl; benzyl; or R^3 and R^4 taken together with the nitrogen to which they are attached form a saturated heterocyclic ring having four or five carbon atoms, with the proviso that R^1 and R^2 can not both be hydrogen. In a preferred embodiment of the present invention, at least one of R^1 and R^2 is a group of the formula II, more preferred R_3 and R_4 are C_1 to C_8 alkyl.

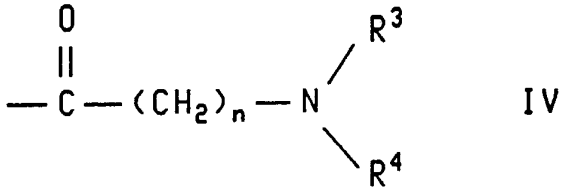
The present invention also relates to intermediates for forming prodrugs of rapamycin of formula I wherein R_1 or R_2 are each independently



III

X is a suitable leaving group, and m is 1 to 6. Preferred leaving groups include, Br, Cl, I, $-OSO_2CH_3$, and p-toluene-sulfonate.

The present invention also relates to prodrugs of rapamycin of formula I wherein R^2 is hydrogen and R^1 is



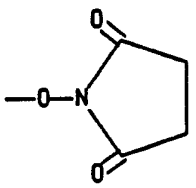
IV

wherein n is 1 to 6; R^3 and R^4 are each independently hydrogen; branch or straight C_1 to C_8 alkyl; cyclic C_3 to C_8 alkyl; phenyl; benzyl; or R^3 and R^4 taken together with the nitrogen to which they are attached to form a saturated heterocyclic ring having four or five carbons atoms, or pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions including the prodrugs.

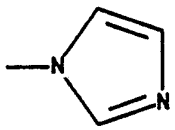
Detailed Description of the Invention

The compounds of formula I are rapamycin prodrugs. Rapamycin and certain prodrugs thereof are described in United States Patents 3,929,992; 3,993,749; 4,316,885; and 4,650,803, the disclosure of which is hereby incorporated herein by reference.

The prodrug compounds of the present invention are produced by first forming the acetate ester of rapamycin. This is accomplished by reacting rapamycin, the compound of formula I where R_1 and R_2 are both hydrogen with an acylating agent of the formula $YCO(CH_2)_mX$ (V) where m is as defined above in the presence of an alkyl amine base and a non-polar solvent. For the acylating agent of formula V, Y is, for example, halogen, N_3, $-O-COCH_2-X$,



, or



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