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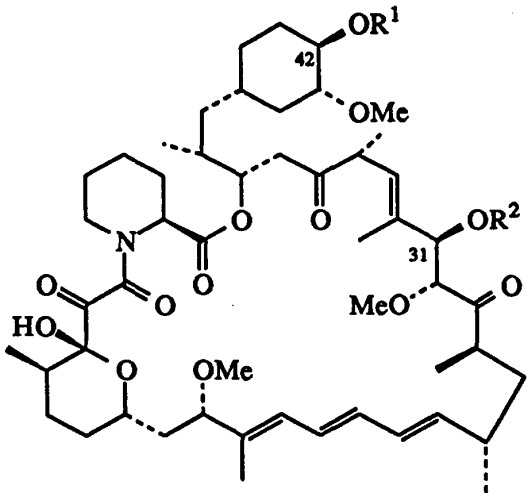
(54) Title: RAPAMYCIN HYDROXYESTERS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

A compound of structure (I) wherein R^1 and R^2 are each, independently, hydrogen or $-CO(CR^3R^4)_b(CR^5R^6)_dCR^7R^8R^9$; R^3 and R^4 are each, independently, hydrogen, alkyl, alkenyle, alkynyl, trifluoromethyl, or -F; R^5 and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or $-CO_2R^{11}$, or R^5 and R^6 may be taken together to form X or a cycloalkyl ring that is optionally mono-, di-, or tri-substituted with $-(CR^3R^4)_fOR^{10}$; R^7 is hydrogen, alkyl, alkenyl, alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or $-CO_2R^{11}$; R^8 and R^9 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, $-(CR^3R^4)_fOR^{10}$, $-CF_3$, -F, or $-CO_2R^{11}$, or R^8 and R^9 may be taken together to form X or a cycloalkyl ring that is optionally mono-, di-, or tri-substituted with $-(CR^3R^4)_fOR^{10}$; R^{10} is hydrogen, alkyl, alkenyl, alkynyl, tri-(alkyl)silyl, tri-(alkyl)silylethyl, triphenylmethyl, benzyl, alkoxymethyl, tri-(alkyl)silylethoxymethyl, chloroethyl, or tetrahydropyranyl; R^{11} is hydrogen, alkyl, alkenyl, alkynyl, or phenylalkyl; X is 5-(2,2-dialkyl)[1,3]dioxanyl, 5-(2-spiro-cycloalkyl)[1,3]dioxanyl, 4-(2,2-dialkyl)[1,3]dioxanyl, 4-(2-spiro-cycloalkyl)[1,3]dioxanyl, 4-(2,2-dialkyl)[1,3]-dioxalanyl, or 4-(2-spiro-cycloalkyl)[1,3]dioxalanyl; b = 0-6; d = 0-6; and f = 0-6 with the proviso that R^1 and R^2 are both not hydrogen and further provided that either R^1 or R^2 contains at least one $-(CR^3R^4)_fOR^{10}$, X, or $-(CR^3R^4)_fOR^{10}$ substituted cycloalkyl group, or a pharmaceutically acceptable salt thereof which is useful as an immunosuppressive, antiinflammatory, antifungal, antiproliferative, and antitumor agent.



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RAPAMYCIN HYDROXYESTERS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

This invention relates to hydroxyesters of rapamycin and a method for using them for inducing immunosuppression, and in the treatment of transplantation rejection, graft vs. host disease, autoimmune diseases, diseases of inflammation, adult T-cell leukemia/lymphoma, solid tumors, fungal infections, and hyperproliferative vascular disorders.

Rapamycin is a macrocyclic triene antibiotic produced by Streptomyces hygroscopicus, which was found to have antifungal activity, particularly against Candida albicans, both in vitro and in vivo [C. Vezina et al., J. Antibiot. 28, 721 (1975); S.N. Sehgal et al., J. Antibiot. 28, 727 (1975); H. A. Baker et al., J. Antibiot. 31, 539 (1978); U.S. Patent 3,929,992; and U.S. Patent 3,993,749].

Rapamycin alone (U.S. Patent 4,885,171) or in combination with picibanil (U.S. Patent 4,401,653) has been shown to have antitumor activity. R. Martel et al. [Can. J. Physiol. Pharmacol. 55, 48 (1977)] disclosed that rapamycin is effective in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); R. Y. Calne et al., Lancet 1183 (1978); and U.S. Patent 5,100,899].

Rapamycin has also been shown to be useful in preventing or treating systemic lupus erythematosus [U.S. Patent 5,078,999], pulmonary inflammation [U.S. Patent 5,080,899], insulin dependent diabetes mellitus [Fifth Int. Conf. Inflamm. Res. Assoc. 121 (Abstract), (1990)], smooth muscle cell proliferation and intimal thickening following vascular injury [Morris, R. J. Heart Lung Transplant 11 (pt. 2): 197 (1992)], adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1], and ocular inflammation [European Patent Application 532,862 A1].

Mono- and diacylated derivatives of rapamycin (esterified at the 28 and 43 positions) have been shown to be useful as antifungal agents (U.S. Patent 4,316,885) and used to make water soluble aminoacyl prodrugs of rapamycin (U.S. Patent

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