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[54] **RAPAMYCIN HYDROXYESTERS**

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C07D 498/16; C07D 7/04

[52] U.S. Cl. **514/63**; 514/291;
540/452; 540/456

[58] Field of Search 540/456, 452; 514/291,
514/63

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,929,992	12/1975	Sehgal et al.	424/122
3,993,749	11/1976	Sehgal et al.	424/122
4,316,885	2/1982	Rakhit	424/122
4,375,464	3/1983	Sehgal et al.	424/122
4,401,653	8/1983	Eng	424/124
4,650,803	3/1987	Stella et al.	540/456
4,885,171	12/1989	Surendra et al.	424/122
5,023,262	6/1991	Caufield et al.	540/456
5,023,263	6/1991	Von Burg	540/456
5,023,264	6/1991	Caufield et al.	514/291
5,078,999	1/1992	Warner et al.	424/122
5,080,899	1/1992	Sturm et al.	424/122
5,091,389	2/1992	Ondeyka et al.	514/291
5,100,883	3/1992	Schiehser	514/183
5,100,899	3/1992	Calne	514/291
5,102,876	4/1992	Caufield	514/183
5,118,677	6/1992	Caufield	514/183
5,118,678	6/1992	Kao et al.	514/183
5,120,842	6/1992	Failli et al.	540/452
5,130,307	7/1992	Failli et al.	514/291
5,138,051	8/1992	Hughes et al.	540/456
5,151,413	9/1992	Caufield et al.	540/456
5,169,851	12/1992	Hughes et al.	514/291
5,177,203	1/1993	Failli et al.	540/456
5,194,447	3/1993	Kao	540/456
5,221,670	6/1993	Caufield	514/183
5,233,036	8/1993	Hughes	540/456

5,260,300	11/1993	Hu	540/456
5,262,423	11/1993	Kao	514/291
5,286,730	2/1994	Caufield et al.	514/291
5,286,731	2/1994	Caufield et al.	514/291
5,302,584	4/1994	Kao et al.	514/291

FOREIGN PATENT DOCUMENTS

507555A1 7/1992 European Pat. Off. 540/456

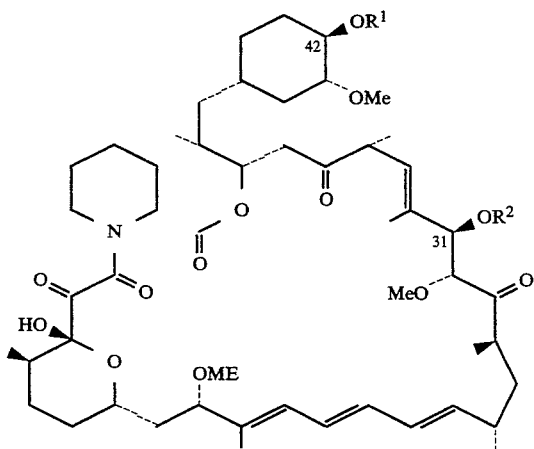
OTHER PUBLICATIONS

Venzina, C., *J. Antibiot.* 28:721 (1975).
 Sehgal, S. N., *J. Antibiot.* 28:727 (1975).
 Baker, H. J., *Antibiot.* 31:539 (1978).
 Martel, R. R., *Can. J. Physiol. Pharmacol.* 55:48 (1977).
 Staruch, M. J., *FASEB* 3:3411 (1989).
 Dumont, F. J., *FASEB* 3:5256 (1989).
 Calne, R. Y., *Lancet* 1183 (1978).
 Morris, R. E., *Med. Sci. Res.* 17:877 (1989).
 Baeder, W. L., *Fifth Int. Conf. Inflamm. Res. Assoc.*
 121 (Abstract) (1990).
 Meiser, B. M., *J. Heart Lung Transplant*, 11 (pt. 2):197
 (1992).
 Stepkowski, S. M., *Transplantation Proc.* 23:507 (1991).

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[57] **ABSTRACT**

A compound of the structure
(Abstract continued on next page.)



wherein R^1 and R^2 are each, independently, hydrogen or $-\text{CO}(\text{CR}^3\text{R}^4)_b(\text{CR}^5\text{R}^6)_d\text{CR}^7\text{R}^8\text{R}^9$;
 R^3 and R^4 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, trifluoromethyl, or $-\text{F}$;
 R^5 and R^6 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, 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 $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$;

R^7 is hydrogen, alkyl, alkenyl, alkynyl, $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$;

R^8 and R^9 are each, independently, hydrogen, alkyl, alkenyl, alkynyl, $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$, 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 $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$;

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-(2,2-dicycloalkyl)[1,3]dioxanyl, 4-(2,2-dialkyl)[1,3]dioxanyl, 4-(2,2-dicycloalkyl)[1,3]dioxanyl, 4-(2,2-dialkyl)[1,3]dioxalanyl, or 4-(2,2-dicycloalkyl)[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 $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$, X, or $-(\text{CR}^3\text{R}^4)_f\text{OR}^{10}$ substituted cycloalkyl group, or a pharmaceutically acceptable salt thereof which is useful as an immunosuppressive, antiinflammatory, antifungal, antiproliferative, and antitumor agent.

24 Claims, No Drawings

RAPAMYCIN HYDROXYESTERS

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. Pat. Nos. 3,929,992; and 3,993,749].

Rapamycin alone (U.S. Pat. No. 4,885,171) or in combination with picibanil (U.S. Pat. No. 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.

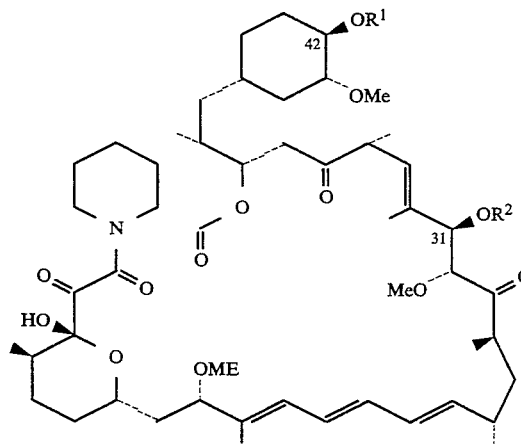
The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); R. Y. Calne et al., Lancet 1183 (1978); and U.S. Pat. No. 5,100,899].

Rapamycin has also been shown to be useful in preventing or treating systemic lupus erythematosus [U.S. Pat. No. 5,078,999], pulmonary inflammation [U.S. Pat. No. 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. Pat. No. 4,316,885) and used to make water soluble aminoacyl prodrugs of rapamycin (U.S. Pat. No. 4,650,803). Recently, the numbering convention for rapamycin has been changed; therefore according to Chemical Abstracts nomenclature, the esters described above would be at the 31- and 42- positions.

DESCRIPTION OF THE INVENTION

This invention provides derivatives of rapamycin which are useful as immunosuppressive, antiinflammatory, antifungal, antiproliferative, and antitumor agents



wherein R¹ and R² are each, independently, hydrogen or —CO(CR³R⁴)_b(CR⁵R⁶)_dCR⁷R⁸R⁹;

R³ and R⁴ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, trifluoromethyl, or —F;

R⁵ and R⁶ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, —(CR³R⁴)_fOR¹⁰, —CF₃, —F, or —CO₂R¹¹, or R⁵ and R⁶ may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with —(CR³R⁴)_fOR¹⁰;

R⁷ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, —(CR³R⁴)_fOR¹⁰, —CF₃, —F, or —CO₂R¹¹;

R⁸ and R⁹ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, —(CR³R⁴)_fOR¹⁰, —CF₃, —F, or —CO₂R¹¹, or R⁸ and R⁹ may be taken together to form X or a cycloalkyl ring of 3-8 carbon atoms that is optionally mono-, di-, or tri-substituted with —(CR³R⁴)_fOR¹⁰;

R¹⁰ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silyl, tri-(alkyl of 1-6 carbon atoms)silylethyl, triphenylmethyl, benzyl, alkoxyethyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silylethoxymethyl, chloroethyl, or tetrahydropyranyl;

R¹¹ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, or phenylalkyl of 7-10 carbon atoms;

X is 5-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 5-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, 4-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxalanyl, or 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxalanyl;

b=0-6;

d=0-6; and

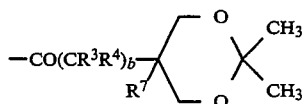
f=0-6

with the proviso that R¹ and R² are both not hydrogen and further provided that either R¹ or R² contains at least one —(CR³R⁴)_fOR¹⁰, X, or —(CR³R⁴)_fOR¹⁰ substituted cycloalkyl of 3-8 carbon atoms group, or a

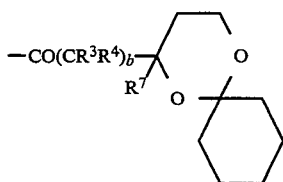
The pharmaceutically acceptable salts are those derived from such inorganic cations such as sodium, potassium, and the like; and organic bases such as: mono-, di-, and trialkyl amines of 1-6 carbon atoms, per alkyl group and mono-, di-, and trihydroxyalkyl amines of 1-6 carbon atoms per alkyl group, and the like.

The terms alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, and alkenyl of 2-7 carbon atoms, include both straight chain as well as branched carbon chains. As the compounds of this invention can contain more than one $-(CR^3R^4)_bOR^{10}$ group, R^3 , R^4 , f , and R^{10} can be the same or different. Similarly, when other generic substituent descriptions are repeated in the same structure, they can be the same or different.

For a compound in which R^1 contains R^8 and R^9 taken together to form X, where X is 5-(2,2-di-(alkyl of 1-6 carbon atoms))[1,3]dioxanyl, the alkyl group of X contains 1 carbon atom, and $d=0$, R^1 would have the following structure.



Similarly, for a compound in which R^1 contains R^8 and R^9 taken together to form X, where X is 4-(2,2-di-(cycloalkyl of 3-8 carbon atoms))[1,3]dioxanyl, the cycloalkyl group of X contains 6 carbon atom, and $d=0$, R^1 would have the following structure.



For compounds containing X, preferred compounds include those in which the alkyl group of X, if present, is methyl and the cycloalkyl group of X, if present, is cyclohexyl.

When R^{10} is not hydrogen, alkyl, alkenyl, or alkenyl, it is intended that R^{10} is a group that can serve as an alcohol protecting group. Thus, these groups are intermediates of free hydroxylated compounds, as well as being biologically active in their own right. R^{10} covers tri-(alkyl of 1-6 carbon atoms)silyl, tri-(alkyl of 1-6 carbon atoms)silylethyl, triphenylmethyl, benzyl, alkoxymethyl of 2-7 carbon atoms, tri-(alkyl of 1-6 carbon atoms)silylethoxymethyl, chloroethyl, and tetrahydropyranyl groups. Other alcohol protecting groups are known by one skilled in the art and are also considered part of this invention.

Of the compounds of this invention preferred members are those in which R^2 is hydrogen; those in which R^2 is hydrogen, $b=0$, and $d=0$; those in which R^2 is hydrogen, $b=0$, $d=0$, and R^8 and R^9 are each, independently hydrogen, alkyl, or $-(CR^3R^4)_bOR^{10}$, or are taken together to form X.

Compounds of this invention having the ester group $-(CO(CR^3R^4)_bCR^5R^6)_d(CR^7R^8R^9)_e$ at the 42- or 31,42-positions can be prepared by acylation of rapamycin using protected hydroxy and polyhydroxy acids, alkoxy or polyalkoxy carboxylic acids that have been acti-

groups, if so desired. Several procedures for carboxylate activation are known in the art, but the preferred methods utilize carbodiimides, mixed anhydrides, or acid chlorides. For example, an appropriately substituted carboxylic acid can be activated as a mixed anhydride, with an acylating group such as 2,4,6-trichlorobenzoyl chloride. Treatment of rapamycin with the mixed anhydride under mildly basic condition provides the desired compounds. Alternatively, the acylation reaction can be accomplished with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and dimethylaminopyridine. Mixtures of 42- and 31,42-esters can be separated by chromatography.

The 31-ester-42-hydroxy compounds of this invention can be prepared by protecting the 42-alcohol of rapamycin with a protecting group, such as with a tert-butyl dimethylsilyl group, followed by esterification of the 31-position by the procedures described above. The preparation of rapamycin 42-silyl ethers is described in U.S. Pat. No. B1 5,120,842, which is hereby incorporated by reference. Removal of the protecting group provides the 31-esterified compounds. In the case of the tert-butyl dimethylsilyl protecting group, deprotection can be accomplished under mildly acidic conditions, such as acetic acid/water/THF. The deprotection procedure is described in Example 15 of U.S. Pat. No. 5,118,678, which is hereby incorporated by reference.

Having the 31-position esterified and the 42-position deprotected, the 42-position can be esterified using a different acylating agent than was reacted with the 31-alcohol, to give compounds having different esters at the 31- and 42- positions. Alternatively, the 42-esterified compounds, prepared as described above, can be reacted with a different acylating agent to provide compounds having different esters at the 31- and 42-positions.

This invention also covers analogous hydroxy esters of other rapamycins such as, but not limited to, 29-demethoxyrapamycin, [U.S. Pat. No. 4,375,464, 32-demethoxyrapamycin under C.A. nomenclature]; rapamycin derivatives in which the double bonds in the 1-, 3-, and/or 5-positions have been reduced [U.S. Pat. No. 5,023,262]; 29-desmethylrapamycin [U.S. Pat. No. 5,093,339, 32-desmethylrapamycin under C.A. nomenclature]; 7,29-bisdesmethylrapamycin [U.S. Pat. No. 5,093,338, 7,32-desmethylrapamycin under C.A. nomenclature]; and 15-hydroxyrapamycin [U.S. Pat. No. 5,102,876]. The disclosures in the above cited U.S. Patents are hereby incorporated by reference.

Immunosuppressive activity for representative compounds of this invention was evaluated in an in vitro standard pharmacological test procedure to measure the inhibition of lymphocyte proliferation (LAF) and in two in vivo standard pharmacological test procedures. The pinch skin graft test procedure measures the immunosuppressive activity of the compound tested as well as the ability of the compound tested to inhibit or treat transplant rejection. The adjuvant arthritis standard pharmacological test procedure, which measures the ability of the compound tested to inhibit immune mediated inflammation. The adjuvant arthritis test procedure is a standard pharmacological test procedure for rheumatoid arthritis. The procedures for these standard pharmacological test procedures are provided below.

The comitogen-induced thymocyte proliferation procedure (LAF) was used as an in vitro measure of the

pounds. Briefly, cells from the thymus of normal BALB/c mice are cultured for 72 hours with PHA and IL-1 and pulsed with tritiated thymidine during the last six hours. Cells are cultured with and without various concentrations of rapamycin, cyclosporin A, or test compound. Cells are harvested and incorporated radioactivity is determined. Inhibition of lymphoproliferation is assessed as percent change in counts per minute from nondrug treated controls. For each compound evaluated, rapamycin was also evaluated for the purpose of comparison. An IC_{50} was obtained for each test compound as well as for rapamycin. When evaluated as a comparator for the representative compounds of this invention, rapamycin had an IC_{50} ranging from 0.6–1.5 nM. The results obtained are provided as an IC_{50} and as the percent inhibition of T-cell proliferation at 0.1 μ M. The results obtained for the representative compounds of this invention were also expressed as a ratio compared with rapamycin. A positive ratio indicates immunosuppressive activity. A ratio of greater than 1 indicates that the test compound inhibited thymocyte proliferation to a greater extent than rapamycin. Calculation of the ratio is shown below.

$$\frac{IC_{50} \text{ of Rapamycin}}{IC_{50} \text{ of Test Compound}}$$

Representative compounds of this invention were also evaluated in an in vivo test procedure designed to determine the survival time of pinch skin graft from male BALB/c donors transplanted to male $C_3H(H-2K)$ recipients. The method is adapted from Billingham R. E. and Medawar P. B., *J. Exp. Biol.* 28:385–402, (1951). Briefly, a pinch skin graft from the donor was grafted on the dorsum of the recipient as an allograft, and an isograft was used as control in the same region. The recipients were treated with either varying concentrations of test compounds intraperitoneally or orally. Rapamycin was used as a test control. Untreated recipients serve as rejection control. The graft was monitored daily and observations were recorded until the graft became dry and formed a blackened scab. This was considered as the rejection day. The mean graft survival time (number of days \pm S.D.) of the drug treatment group was compared with the control group. The following table shows the results that were obtained. Results are expressed as the mean survival time in days. Untreated (control) pinch skin grafts are usually rejected within 6–7 days. Compounds were tested using a dose of 4 mg/kg.

The adjuvant arthritis standard pharmacological test procedure measures the ability of test compounds to prevent immune mediated inflammation and inhibit or treat rheumatoid arthritis. The following briefly describes the test procedure used. A group of rats (male inbred Wistar Lewis rats) are pre-treated with the compound to be tested (1 h prior to antigen) and then injected with Freud's Complete Adjuvant (FCA) in the right hind paw to induce arthritis. The rats are then orally dosed on a Monday, Wednesday, Friday schedule from day 0–14 for a total of 7 doses. Both hind paws are measured on days 16, 23, and 30. The difference in paw volume (mL) from day 16 to day 0 is determined and a percent change from control is obtained. The left hind paw (uninjected paw) inflammation is caused by T-cell mediated inflammation and is recorded in the above table (% change from control). The right hind

specific inflammation. Compounds were tested at a dose of 5 mg/kg. The results are expressed as the percent change in the uninjected paw at day 16 versus control; the more negative the percent change, the more potent the compound. Rapamycin provided between –70% and –90% change versus control, indicating that rapamycin treated rats had between 70–90% less immune induced inflammation than control rats.

The results obtained in these standard pharmacological test procedures are provided following the procedure for making the specific compounds that were tested.

The results of these standard pharmacological test procedures demonstrate immunosuppressive activity both in vitro and in vivo for the compounds of this invention. The results obtained in the LAF test procedure indicates suppression of T-cell proliferation, thereby demonstrating the immunosuppressive activity of the compounds of this invention. Further demonstration of the utility of the compounds of this invention as immunosuppressive agents was shown by the results obtained in the skin graft and adjuvant arthritis standard pharmacological test procedures. Additionally, the results obtained in the skin graft test procedure further demonstrates the ability of the compounds of this invention to treat or inhibit transplantation rejection. The results obtained in the adjuvant arthritis standard pharmacological test procedure further demonstrate the ability of the compounds of this invention to treat or inhibit rheumatoid arthritis.

Based on the results of these standard pharmacological test procedures, the compounds are useful in the treatment or inhibition of transplantation rejection such as kidney, heart, liver, lung, bone marrow, pancreas (islet cells), cornea, small bowel, and skin allografts, and heart valve xenografts; in the treatment or inhibition of autoimmune diseases such as lupus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, and multiple sclerosis; and diseases of inflammation such as psoriasis, dermatitis, eczema, seborrhea, inflammatory bowel disease, pulmonary inflammation (including asthma, chronic obstructive pulmonary disease, emphysema, acute respiratory distress syndrome, bronchitis, and the like), and eye uveitis.

Because of the activity profile obtained, the compounds of this invention also are considered to have antitumor, antifungal activities, and antiproliferative activities. The compounds of this invention therefore also useful in treating solid tumors, adult T-cell leukemia/lymphoma, fungal infections, and hyperproliferative vascular diseases such as restenosis and atherosclerosis. When used for restenosis, it is preferred that the compounds of this invention are used to treat restenosis that occurs following an angioplasty procedure. When used for this purpose, the compounds of this invention can be administered prior to the procedure, during the procedure, subsequent to the procedure, or any combination of the above.

When administered for the treatment or inhibition of the above disease states, the compounds of this invention can be administered to a mammal orally, parenterally, intranasally, intrabronchially, transdermally, topically, intravaginally, or rectally.

It is contemplated that when the compounds of this invention are used as an immunosuppressive or anti-inflammatory agent, they can be administered in conjunction

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