



US005391730A

United States Patent [19][11] **Patent Number:** **5,391,730**

Skotnicki et al.

[45] **Date of Patent:** **Feb. 21, 1995**[54] **PHOSPHORYLCARBAMATES OF RAPAMYCIN AND OXIME DERIVATIVES THEREOF**[75] **Inventors:** **Jerauld S. Skotnicki, Allentown; Andri L. Smith, Princeton, both of N.J.**[73] **Assignee:** **American Home Products Corporation, Madison, N.J.**[21] **Appl. No.:** **134,428**[22] **Filed:** **Oct. 8, 1993**[51] **Int. Cl.⁶** **A61K 31/395; C07D 491/06**[52] **U.S. Cl.** **540/456**[58] **Field of Search** **540/456; 514/291**[56] **References Cited****U.S. PATENT DOCUMENTS**

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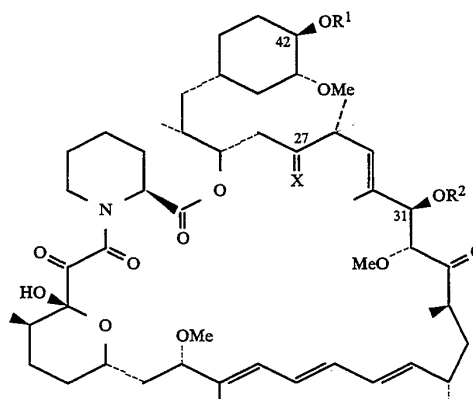
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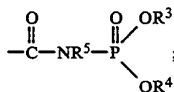
Stepkowski, S. M. *Transplantation Proc.* 23:507 (1991).*Primary Examiner*—Robert T. Bond*Attorney, Agent, or Firm*—Arnold S. Milowsky[57] **ABSTRACT**

A compound of the structure



(Abstract continued on next page.)

wherein R¹ and R² are each, independently, hydrogen, or



R³ and R⁴ are each, independently, hydrogen, Ar, or $-(\text{CR}^6\text{R}^7)_a\text{Y}(\text{CR}^8\text{R}^9)_b\text{Z}$, or R³ and R⁴ may be taken together to form a 5-7 membered ring;

R⁵ is hydrogen, alkyl, alkenyl, alkynyl, alkoxyalkyl, arylalkyl, cycloalkyl, or Ar;

R⁶, R⁷, R⁸, and R⁹, are each, independently, hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, alkylthioalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylalkyl, cycloalkyl, $-\text{OR}^{10}$, $-\text{SR}^{10}$, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{COR}^{10}$, $-\text{CO}_2\text{R}^{10}$, $-\text{CONHR}^{10}$, $-\text{SO}_2\text{R}^{10}$, $-\text{SO}_3\text{R}^{10}$, $-\text{OSO}_3\text{R}^{10}$, $-\text{NR}^{10}\text{R}^{11}$, $-\text{NHCOR}^{10}$, $-\text{NHCO}_2\text{R}^{10}$, $-\text{NHSO}_2\text{R}^{10}$, $-\text{NHSO}_3\text{R}^{10}$, or Ar;

X is 0 or NOR¹²;

Y is $-\text{O}-$, $-\text{CH}_2-$, $-\text{NR}^{13}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, or $-\text{C}(\text{O})-$;

R¹⁰, R¹¹, R¹², and R¹³ are each, independently, hydrogen, alkyl, or arylalkyl;

Z is hydrogen, alkyl of 1-6 carbon atoms, or Ar;

Ar is aryl which may be optionally mono-, di-, or tri-substituted;

a = 1-6 and;

b = 0-6;

or a pharmaceutically acceptable salt thereof, with the proviso that R¹ and R² are not both hydrogen; and further provided that when a is greater than 1, each of the (CR⁶R⁷) subunits may be the same or different and when b is greater than 1, each of the (CR⁸R⁹) may be the same or different which is useful as an immunosuppressive, antiinflammatory, antifungal, antiproliferative, and antitumor agent.

9 Claims, No Drawings

PHOSPHORYLCARBAMATES OF RAPAMYCIN AND OXIME DERIVATIVES THEREOF

BACKGROUND OF THE INVENTION

This invention relates to phosphorylcarbamates of rapamycin and oxime derivatives thereof and a method for using them for inducing immunosuppression, and in the treatment of transplantation rejection, host vs. graft disease, autoimmune diseases, diseases of inflammation, 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. No. 3,929,992; and U.S. Pat. No. 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.

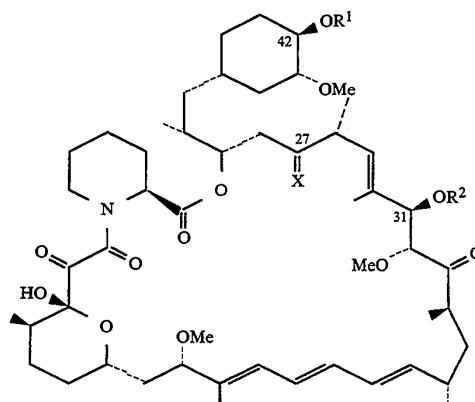
The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); 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. 21 (Abstract), (1990)], and smooth muscle cell proliferation and intimal thickening following vascular injury [Morris, R. J. Heart Lung Transplant 11 (pt. 2): 197 (1992)].

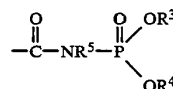
Mono- and diacylated derivatives of rapamycin (esterified at the 28 and 43 positions) have been shown to be useful as antifungal agents (U.S. Pat. No. 4,316,885) and used to make water soluble prodrugs of rapamycin (U.S. Pat. No. 4,650,803). Recently, the numbering convention for rapamycin has been changed; therefore according to Chemical Abstracts nomenclature, the esters described above would be at the 31- and 42-positions. U.S. Pat. No. 5,118,678 discloses carbamates of rapamycin that are useful as immunosuppressive, anti-inflammatory, antifungal, and antitumor agents. U.S. Pat. No. 5,194,447 discloses sulfonyl carbamates useful as immunosuppressive, anti-inflammatory, antifungal, and antitumor agents. U.S. Pat. No. 5,023,264 discloses oximes of rapamycin useful as immunosuppressive, anti-inflammatory, and antifungal agents.

DESCRIPTION OF THE INVENTION

This invention provides derivatives of rapamycin which are useful as immunosuppressive, anti-inflammatory, antifungal, antiproliferative, and antitumor agents having the structure



wherein R¹ and R² are each, independently, hydrogen, or



R³ and R⁴ are each, independently, hydrogen, Ar, or $-(CR^6R^7)_aY(CR^8R^9)_bZ$, or R³ and R⁴ may be taken together to form a 5-7 membered ring;

R⁵ is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkoxyalkyl of 2-7 carbon atoms, arylalkyl of 7-10 carbon

atoms, cycloalkyl of 3-8 carbon atoms, or Ar;

R⁶, R⁷, R⁸, and R⁹, are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkenyl of 2-7 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, alkoxyalkyl of 2-12 carbon atoms, alkylthioalkyl of 2-12 carbon atoms, alkylaminoalkyl of 2-12 carbon atoms, dialkylaminoalkyl of 3-12 carbon atoms, arylalkyl of 7-10 carbon atoms, cycloalkyl of 3-8 carbon atoms, $-OR^{10}$, $-SR^{10}$, halogen, $-CN$, $-NO_2$, $-CF_3$, $-COR^{10}$, $-CO_2R^{10}$, $-CONHR^{10}$, $-SO_2R^{10}$, $-SO_3R^{10}$, $-OSO_3R^{10}$, $-NR^{10}R^{11}$, $-NHCOR^{10}$, $-NHCO_2R^{10}$, $-NHSO_2R^{10}$, $-NHSO_3R^{10}$, or Ar;

X is O or NOR¹²;

Y is $-O-$, $-CH_2-$, $-NR^{13}-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-C(O)-$;

R¹⁰, R¹¹, R¹², and R¹³ are each, independently, hydrogen, alkyl of 1-6 carbon atoms, or arylalkyl of 7-10 carbon atoms;

Z is hydrogen, alkyl of 1-6 carbon atoms, or Ar;

Ar is aryl which may be optionally mono-, di-, or tri-substituted with a group selected from alkyl of 1-6 carbon atoms, arylalkyl of 7-10 carbon atoms, alkoxy of 1-6 carbon atoms, cyano, halo, hydroxy, nitro, carbalkoxy of 2-7 carbon atoms, trifluoromethyl, amino, dialkylamino of 1-6 carbon atoms per alkyl group, dialkylaminoalkyl of 3-12 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, alkoxyalkyl of 2-12 carbon atoms, alkylthio of 1-6 carbon atoms, $-SO_3H$, $-PO_3H$, and $-CO_2H$;

a=1-6 and;

b=0-6;

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or a pharmaceutically acceptable salt thereof, with the proviso that R^1 and R^2 are not both hydrogen; and further provided that when a is greater than 1, each of the (CR^6R^7) subunits may be the same or different and when b is greater than 1, each of the (CR^8R^9) may be the same or different.

It is preferred that the aryl moiety of the Ar group or of the arylalkyl group is a phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, quinoxalyl, thienyl, thionaphthyl, furyl, benzofuryl, benzodioxyl, benzoxazolyl, benzisoxazolyl, indolyl, thiazolyl, isoxazolyl, pyrimidinyl, pyrazinyl, benzopyranlyl, benz[b]thiophenolyl, benzimidazolyl, benzthiazolyl, benzodioxolyl, piperidyl, morpholinyl, piperazinyl, tetrahydrofuranlyl, or pyrrolidinyl group which may be optionally mono-, di-, or tri-substituted with a group selected from alkyl of 1-6 carbon atoms, arylalkyl of 7-10 carbon atoms, alkoxy of 1-6 carbon atoms, cyano, halo, hydroxy, nitro, carbalkoxy of 2-7 carbon atoms, trifluoromethyl, amino, dialkylamino of 1-6 carbon atoms per alkyl group, dialkylaminoalkyl of 3-12 carbon atoms, hydroxyalkyl of 1-6 carbon atoms, alkoxyalkyl of 2-12 carbon atoms, alkylthio of 1-6 carbon atoms, $-SO_3H$, $-PO_3H$, and $-CO_2H$. It is more preferred that the aryl moiety is a phenyl group that may be optionally substituted as described above.

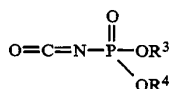
When R^3 and R^4 are defined as being taken together to form a 5-7 membered ring, it is preferred that R^3R^4 are $-(CH_2)_2-$, $-(CH_2)_3-$, or $-(CH_2)_4-$.

When X is NOR¹³, the 27-oxime can exist in both the E and the Z forms; this disclosure covers both of these forms.

The pharmaceutically acceptable salts are those derived from such inorganic cations such as sodium, potassium, and the like; 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; and organic and inorganic acids as: acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids.

Of these compounds, preferred members are those in which R^3 and R^4 are alkyl of 1-6 carbon atoms; those in which R^5 is hydrogen; those in which R^2 and R^5 are hydrogen; and those in which R^2 and R^5 are hydrogen and R^3 and R^4 are alkyl of 1-6 carbon atoms.

The compounds of this invention in which R^5 is hydrogen, that are carbamylated at the 42-position or at both the 31- and 42-positions can be prepared by reacting rapamycin with an isocyanate having the general structure



either in the presence of a base, such as pyridine, or in the absence of a base.

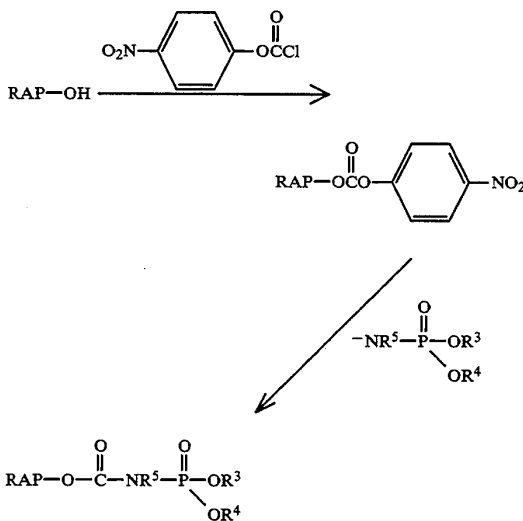
The 31-carbamylated compounds of this invention in which R^5 is hydrogen can be prepared by protecting the 42-alcohol of rapamycin with a protecting group, such as with a tert-butyl dimethylsilyl group, followed by carbamylation of the 31-position with an isocyanate with the general structure shown above. Removal of the protecting group provides the 31-carbamylated compounds. In the case of the tert-butyl dimethylsilyl

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protecting group, deprotection can be accomplished under mildly acidic conditions. The protection and deprotection of the 42-hydroxyl group of rapamycin was disclosed in U.S. Pat. No. 5,120,842, which is hereby incorporated by reference.

Having the 31-position carbamylated and the 42-position deprotected, the 42-position can be reacted with a different isocyanate than was reacted with the 31-alcohol, to give compounds having different carbamates at the 31- and 42-positions. Alternatively, the 42-carbamylated compounds, prepared as described above, can be reacted with a different isocyanate to provide compounds having different carbamates at the 31- and 42-positions.

For the compounds of this invention in which R^5 is hydrogen or is a substituent other than hydrogen, carbamates can be formed at the 42- and at the 31- and 42-positions by first converting rapamycin to a carbonate by reacting rapamycin with a suitable chloroformate, such as p-nitrophenyl chloroformate, followed by reaction of the carbonate with an appropriately substituted phosphoramidate anion, as shown in the scheme below.



The phosphoramidate anion can be generated by treating the appropriate phosphoramidate with a strong base, such as sodium hydride or lithium diisopropylamide, at low temperatures, typically $-78^\circ C$. The 31-carbamylated compounds of this invention can be prepared using this route by first protecting the 42-position as described above, followed by conversion of the 31-hydroxyl group to a carbonate and subsequent treatment with a phosphoramidate anion.

For the compounds of this invention in which X is NOR¹², the oximation of the 27-ketone of rapamycin can be accomplished following the carbamylation by treatment of the rapamycin phosphonylcarbamate with an appropriately substituted hydroxylamine, as disclosed in U.S. Pat. No. 5,023,264, which is hereby incorporated by reference.

The isocyanates, phosphoramidates, and hydroxylamines used to prepare the compounds of the invention are commercially available or can be prepared by methods that are disclosed in the literature.

This invention also covers analogous carbamates 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]; 42-oxorapamycin [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-hydroxy- and 15,27-bishydroxy-rapamycin [U.S. Pat. No. 5,102,876]. The disclosures in the above cited U.S. Patents are hereby incorporated by reference.

This invention additionally covers derivatives of rapamycin in which one of the 31- or 42-hydroxyl groups has been converted to a phosphorylcarbamate, as described above, and the other of the 31- or 42-hydroxyl groups has been esterified with a moiety that is not a phosphonylcarbamate. Such other esters include acyl derivatives of rapamycin as described in U.S. Pat. No. 4,316,885, which is hereby incorporated by reference; fluorinated esters of rapamycin as described in U.S. Pat. No. 5,100,883, which is hereby incorporated by reference; amide esters of rapamycin as described in U.S. Pat. No. 5,118,677, which is hereby incorporated by reference; carbamates of rapamycin as described in U.S. Pat. No. 5,118,678, which is hereby incorporated by reference; aminoesters of rapamycin as described in U.S. Pat. No. 5,130,337, which is hereby incorporated by reference; ethers and acetals of rapamycin as described in U.S. Pat. No. 5,151,413, which is hereby incorporated by reference; aminoacyl esters of rapamycin as described in U.S. Pat. No. 4,650,803, which is hereby incorporated by reference; sulfonates and sulfamates of rapamycin as described in U.S. Pat. No. 5,117,203; silyl ethers of rapamycin as described in U.S. Pat. No. 5,120,842, which is hereby incorporated by reference; and sulfonylcarbamates of rapamycin as described in U.S. Pat. No. 5,194,447, which is hereby incorporated by reference. Similarly, this invention covers compounds in which one hydroxyl of rapamycin has been converted to a phosphonyl carbamate and the other hydroxyl is an inorganic ester of the hydroxyl group. These esters include phosphate, nitrate, sulfinate, sulfonate esters, and the like, and organic esters of these inorganic acids.

Immunosuppressive activity for representative compounds of this invention was evaluated in an in vitro standard pharmacological test procedure to measure lymphocyte proliferation (LAF) and in an in vivo standard pharmacological test procedure which evaluated the survival time of a pinch skin graft.

The mitogen-induced thymocyte proliferation procedure (LAF) was used as an in vitro measure of the immunosuppressive effects of representative compounds. 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 IC₅₀ 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 IC₅₀ ranging from 0.4–5.1 nM. The results obtained are provided as an IC₅₀ and as the percent inhibition of T-cell proliferation at 0.1 μM. 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 C₃H(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 ± 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. The results shown in Table 1 are based on a dose of 4 mg/kg of test compound. A survival time of 12.0 ± 1.7 days was obtained for rapamycin at 4 mg/kg.

The following table summarizes the results of representative compounds of this invention in these two standard test procedures.

TABLE 1

Compound	EVALUATION OF IMMUNOSUPPRESSIVE ACTIVITY*			
	IC ₅₀ (nM)	LAF		Skin Graft
		(ratio)	% Inhib.+	(days ± SD)
Example 1	90.9	0.04	72	7.2 ± 0.4
Example 2	10.0	0.44	95	10.2 ± 0.4
				10.0 ± 0.6
Example 3	99.0	0.05	51	
Example 4	41.9	0.01	82	

*Calculation of the ratio was described supra.

+Percent inhibition of T-cell proliferation at 0.1 μM.

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. The results obtained for representative compounds of this invention in preventing skin graft rejection further demonstrates their utility as immunosuppressive agents.

Based on the results of these standard pharmacological test procedures, the compounds are useful in the

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