US005434260A

# United States Patent [19]

Skotnicki et al.

[11] Patent Number: 5,434,260

[45] Date of Patent: Jul. 18, 1995

[54] **CARBAMATES OF RAPAMYCIN**

[75] Inventors: **Jerauld S. Skotnicki**, Allentown, N.J.; **Yvette L. Palmer**, Newtown, Pa.; **Wenling Kao**, Paoli, Pa.; **Magid A. Abou-Gharbia**, Glen Mills, Pa.

[73] Assignee: **American Home Products Corporation**, Madison, N.J.

[21] Appl. No.: **259,701**

[22] Filed: **Jun. 14, 1994**

**Related U.S. Application Data**

[60] Continuation-in-part of Ser. No. 160,984, Dec. 1, 1993, abandoned, which is a division of Ser. No. 54,655, Apr. 23, 1993, Pat. No. 5,302,584, which is a continuation-in-part of Ser. No. 960,597, Oct. 13, 1992, abandoned.

[51] **Int. Cl.**[6] ..... **A61K 31/395**; C07D 498/04

[52] **U.S. Cl.** ..... **514/291**; 540/452; 540/456; 514/212; 514/218; 514/222.5; 514/229.2; 514/233.2; 514/242; 514/241; 514/253

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

[56] **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 3,929,992 | 12/1975 | Sehgal et al. | 424/122 |
| 3,993,749 | 11/1976 | Seugal 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 | 424/114 |
| 4,650,803 | 3/1987 | Stella et al. | 514/291 |
| 4,885,171 | 12/1989 | Surendra et al. | 424/122 |
| 5,023,262 | 6/1991 | Caufield et al. | 514/291 |
| 5,023,263 | 6/1991 | Von Burg | 514/291 |
| 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 |
| 5,100,863 | 3/1992 | Schiehser | 514/183 |
| 5,100,899 | 3/1992 | Calne | 514/291 |
| 5,102,876 | 4/1992 | Caufield | 544/456 |
| 5,118,677 | 6/1992 | Caufield | 540/456 |
| 5,118,678 | 6/1992 | Kao et al. | 540/456 |
| B1 5,120,842 | 7/1993 | Failli et al. | 540/456 |
| 5,120,842 | 6/1992 | Failli et al. | 540/456 |
| 5,130,307 | 7/1992 | Failli et al. | 540/456 |
| 5,138,051 | 8/1992 | Hughes et al. | 540/456 |
| 5,151,413 | 9/1992 | Caufield et al. | 514/63 |
| 5,169,851 | 12/1992 | Hughes et al. | 540/456 |
| 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 | 540/455 |
| 5,260,300 | 11/1993 | Hu | 540/456 |
| 5,262,423 | 11/1993 | Kao | 540/456 |
| 5,286,730 | 2/1994 | Caufield et al. | 514/291 |
| 5,286,731 | 2/1994 | Caulfield et al. | 514/291 |
| 5,302,584 | 4/1992 | Kao et al. | 540/456 |

FOREIGN PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 507555 | 10/1992 | European Pat. Off. | 514/291 |
| WO91/13899 | 9/1991 | WIPO | 540/456 |

OTHER PUBLICATIONS

Vezina et al. "J of Antibiotics", vol. 28, pp. 221–226 (1975).

Sehgal et al. "J. of Antibiotics", vol. 28, pp. 727–732 (1975).

Baker et al. "J. of Antibiotics", vol. 31, pp. 539–545 (1978.

Stepkonuski "Transplantation Proceedings" vol. 23, No. 1 (1991) pp. 507–508.

Galne et al. "The Lancet" Jun. 3, 1978 pp. 1183–1185.

Morris et al. "Med. Sci Res." vol. 17 pp. 877–878 (1989).

Martel et al, "Can J. Physiology and Pharmacology" vol. 55 pp. 48–51 (1977).

Staruch et al. FASEB vol. 3, p. 3477 (1989).

Staruch et al FASEB vol. 3, p. 5256 (1989).

(Abstract) Fifth Int Conf Infamm. Res. Assoc. p. 121 (1990).

(Abstract) J. Heart and Lung Transplantation vol. 11 pt 2 (1992).

*Primary Examiner*—Robert T. Bond

*Attorney, Agent, or Firm*—Arnold S. Milowsky

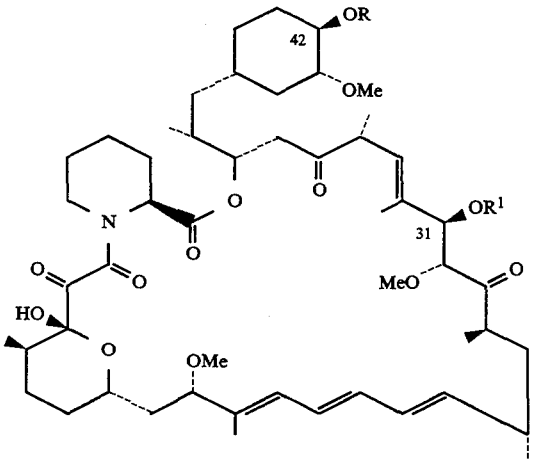
[57] **ABSTRACT**

A compound of the structure

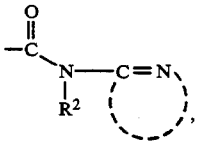
(Abstract continued on next page.)

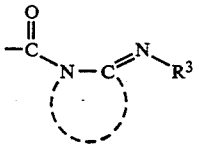
Abstract—continued

II

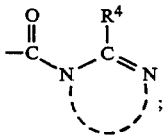


wherein R and $R^1$ are each, independently, hydrogen,





, or

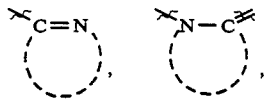


;

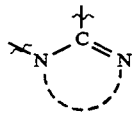
$R^2$ and $R^3$ are each, independently, hydrogen, alkyl, alkenyl, alkynyl. $—CO_2R^5$, $—COR^5$, —CN, $—NO_2$, $—SO_2R^5$, $—SO_3R^5$, $—OR^5$, $—SR^5$, or Ar;

$R^4$ is hydrogen, alkyl, alkenyl, alkynyl, —CF3, $—NR^5R^6$, $—CO_2R^5$, $—COR^5$, $CONR^5R^6$, $—NO_2$, halogen, $—OR^5$, $—SR^5$, —CN, $—SO_2R^5$, $—SO_3R^5$, $—SO_2NR^5R^6$, or Ar;

$R^5$ and $R^6$ are each, independently, hydrogen, alkyl, alkenyl, alkynyl, or Ar;



and



are each, independently, a 5–7 membered saturated, unsaturated, or partially unsaturated heterocyclic radical, that is optionally fused to a phenyl ring or a cycloalkane or cycloalkene ring, wherein the heterocyclic ring may optionally contain O, S, or $NR^8$ in the heterocyclic ring, and may be optionally substituted by $R^7$;

$R^7$ is alkyl of 1–6 carbon atoms, alkenyl, alkynyl, $—CF_3$, $—NR^5R^6$, $—CO_2R^5$, $—COR^5$, $CONR^5R^6$, $—NO_2$, halogen, $—OR^5$, $—SR^5$, —CN, $—SO_2R^5$, $—SO_3R^5$, $—SO_2NR^5R^6$, or Ar;

$R^8$ is hydrogen, alkyl, alkenyl, alkynyl, $—CF_3$, $—NR^5R^6$, $—CO_2R^5$, $—COR^5$, $CONR^5R^6$, $—OR^5$, $—SR_5$, —CN, $—SO_2R^5$, $—SO_3R^5$, $—SO_2NR^5R^6$, or Ar;

Ar is phenyl, naphthyl, or hetaryl, wherein the foregoing may be optionally substituted; with the proviso that R and $R^1$ are both not hydrogen, or a pharmaceutically acceptable salt thereof, which is useful as an immunosuppressive, antiinflammatory, antifungal, antiproliferative, and antitumor agent.

**1 Claim, No Drawings**

# CARBAMATES OF RAPAMYCIN

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of Ser. No. 08/160,984, filed Dec. 1, 1993 abandoned, which is a divisional of Ser. No. 08/054,655, filed Apr. 23, 1993 (now U.S. Pat. No. 5,302,584), which is a continuation in part of Ser. No. 07/960,597, filed Oct. 13, 1992 now abandoned.

## BACKGROUND OF THE INVENTION

This invention relates to carbamates 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, 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.

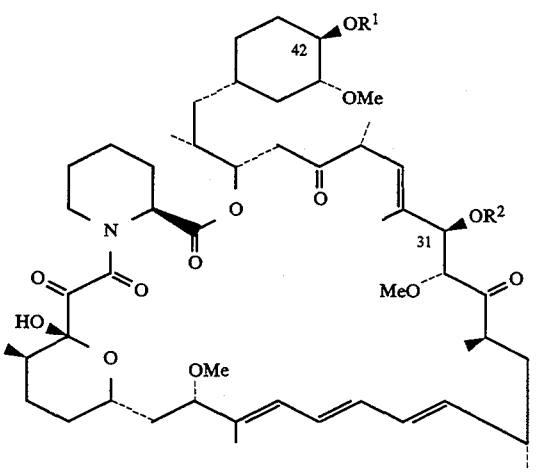
The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); 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. 121 (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.

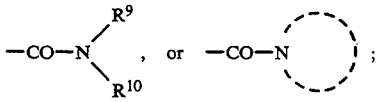
## DESCRIPTION OF THE INVENTION

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




I

wherein $R^1$ and $R^2$ are each, independently, hydrogen, —CONH—$[(CR^3R^4)_m(—A—(CR^5R^6)_n)_p]_q$—B;




$R^3$, $R^4$, $R^5$, $R^6$, and B are each, independently, hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl 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, —$OR^7$, —$SR^7$, halogen, —CN, —$NO_2$, —$CF_3$, —$COR^7$, —$CO_2R^7$, —$CONHR^7$, —$SO_2R^7$, —$OSO_3R^7$, —$NR^7R^8$, —$NHCOR^7$, —$NHSO_2R^7$, or Ar;

$R^7$ and $R^8$ am each, independently, hydrogen, alkyl of 1–6 carbon atoms, arylalkyl of 7–10 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl 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, cycloalkyl of 3–8 carbon atoms, or Ar;

$R^9$ and $R^{10}$ are each, independently, alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl 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, —$CF_3$, —$COR^7$, —$CO_2R^7$, —$CONHR^7$, —$SO_2R^7$, or Ar;

A is —$CH_2$—, —$NR^7$—, —O—, —S—, —SO-, —$SO_2$—, —$PR^7$—, —CO—, —NHCO—, —NHSO—, or —P(O)($R^7$)—;

Ar is phenyl, naphthyl, pyridyl, quinolyl, isoquinolyl, quinoxalyl, thienyl, thionaphthyl, furyl, benzofuryl, benzodioxyl, benzoxazolyl, benzoisoxazolyl, indolyl, thiazolyl, isoxazolyl, pyrimidinyl, pyrazinyl, imidazolyl, benzopyranyl, benz[b]thiopheno-

lyl, benzimidazolyl, benzthiazolyl, benzodioxolyl, piperidinyl, morpholinyl, piperazinyl, tetrahydrofuranyl, or pyrrolidinyl; wherein the Ar group may be optionally mono-, di-, or trisubstituted 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 —$CO_2H$;

is a nitrogen containing hetcrocycle that may be saturated, unsaturated, or partially unsaturated, and 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 —$CO_2H$;

with the proviso that $R^1$ and $R^2$ are not both hydrogen;

m=0–6;

n=0–6;

p=0–1;

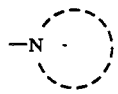
q=0–1;

or a pharmaceutically acceptable salt thereof.

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.

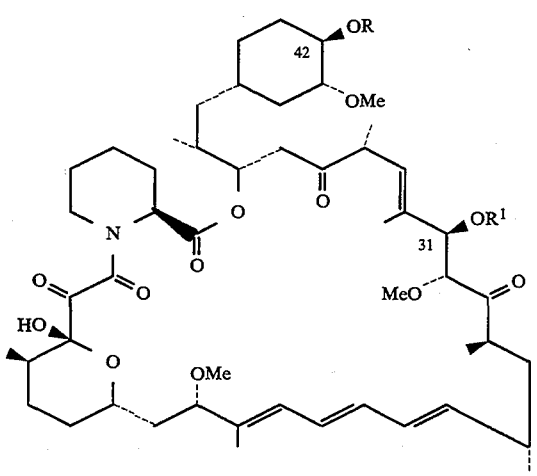
It is preferred that the aryl portion of the arylalkyl substituent is a phenyl, piperazinyl, piperidinyl, or pyridyl group that is optionally mono-, di-, or tri-substituted with a group selected from alkyl of 1–6 carbon atoms, arylalkyl of 7–10 carbon atoms, alkoxy of 1–6 carbon atoms, cyano, halo, nitro, carbalkoxy of 2–7 carbon atoms, trifluoromethyl, amino, dialkylamino of 1–6 carbon atoms per alkyl group, alkylthio of 1–6 carbon atoms, —$SO_3H$, —$PO_3H$, and —$CO_2H$. The term alkyl includes both straight chain and branched alkyl groups.

It is preferred that



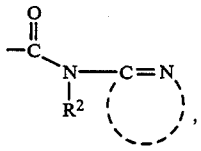
is a pyridyl, pyrazinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolidinyl, thiazolyl, pyrimidinyl, isoxazolyl, pyrrolidinyl, or imidazolyl group that may be optionally substituted as described above.

This invention also discloses preferred amidino carbamates having the structure



II

wherein R and $R^1$ are each, independently, hydrogen,



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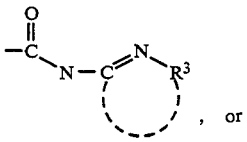

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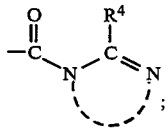
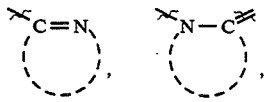


;

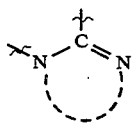
$R^2$ and $R^3$ are each, independently, hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl of 2–7 carbon atoms, —$CO_2R^5$, —$COR^5$, —CN, —$NO_2$, —$SO_2R^5$, —$SO_3R^5$, —$OR^5$, —$SR^5$, or Ar;

$R^4$ is hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl of 2–7 carbon atoms, —$CF_3$, —$NR^5R^6$, —$CO_2R^5$, —$COR^5$, $CONR^5R^6$, —$NO_2$, halogen, —$OR^5$, —$SR^5$, —CN, —$SO_2R^5$, —$SO_3R^5$, —$SO_2NR^5R^6$, or Ar;

$R^5$ and $R^6$ are each, independently, hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl of 2–7 carbon atoms, or Ar;



, and



are each, independently, a 5–7 membered saturated, unsaturated, or partially unsaturated hetero-

cyclic radical, that is optionally fused to a phenyl ring or a cycloalkane or cycloalkene ring of 5–7 carbon atoms, wherein the heterocyclic ring may optionally contain O, S, or $NR^8$ in the heterocyclic ring, and may be optionally substituted by $R^7$;

$R^7$ is alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl of 2–7 carbon atoms, $—CF_3$, $—NR^5R^6$, $—CO_2R^5$, $—COR^5$, $CONR^5R^6$, $—NO_2$, halogen, $—OR^5$, $—SR^5$, —CN, $—SO_2R^5$, $—SO_3R^5$, $—SO_2NR^5R^6$, or Ar;

$R^8$ is hydrogen, alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl of 2–7 carbon atoms, $—CF_3$, $—NR^5R^6$, $—CO_2R^5$, $—COR^5$, $CONR^5R^6$, $—OR^5$, $—SR^5$, —CN, $—SO_2R^5$, $—SO_3R^5$, $—SO_2NR^5R^6$, or Ar;

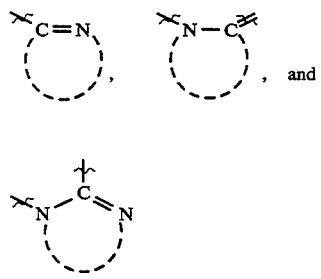
Ar is phenyl, naphthyl, or hetaryl, wherein the foregoing may be optionally mono-, di-, or tri-substituted with a group selected from alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, alkynyl of 2–7 carbon atoms, arylalkyl of 7–10 carbon atoms, alkoxy of 1–6 carbon atoms, cyano, halo, hydroxy, nitro, carbalkoxy of 2–7 carbon atoms, trifluoromethyl, trifluoromethoxy, 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, $—SO_3H$, and $—CO_2H$;

with the proviso that R and $R^1$ are both not hydrogen, or a pharmaceutically acceptable salt thereof.

For the compounds having structure II (immediately above), the terms alkyl of 1–6 carbon atoms, alkenyl of 2–7 carbon atoms, and alkynyl of 2–7 carbon atoms, include both straight chain as well as branched carbon chains. When any of the generic terms (i.e., $R^5$) are contained more than once in a given compound, each may be the same or different. The pharmaceutically acceptable salts of the compounds having structure II are the same as was defined following the compounds of structure I.

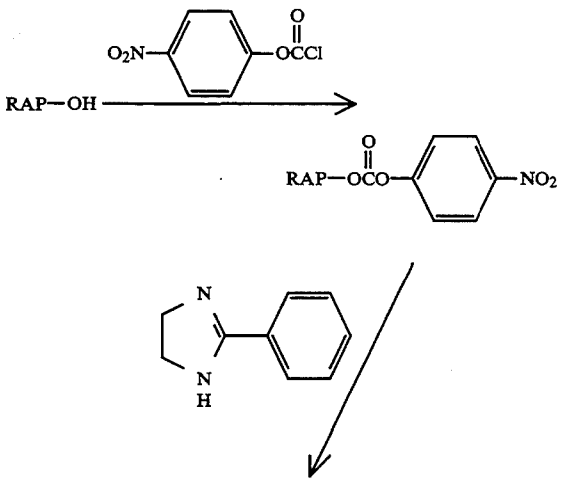
For the compounds having structure II, hetaryl is defined as an unsaturated or partially saturated heterocyclic radical of 5–12 atoms having 1 ring or 2 fused rings. Preferred heterocyclic radicals include unsaturated heterocyclic radicals such as furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 1,2,3-oxathiolyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 1,2,5-oxathiazolyl, 1,3-oxathiolyl, 1,2-pyranyl, 1,4-pyranyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,2,4-oxazinyl, 1,3,2-oxazinyl, 1,2,6-oxazinyl, 1,4-oxazinyl, isoxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,3,5,2-oxadiazinyl, azepinyl, oxepinyl, thiepinyl, 1,2,4-diazepinyl, benzofuranyl, isobenzofuranyl, thionaphthenyl, indolyl, indolenyl, 2-isobenzazolyl, 1,5-pyrindinyl, pyrano[3,4-b]pyrrolyl, benzpyrazolyl, benzisoxazolyl, benzoxazolyl, anthranilyl, 1,2-benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridinyl, pyrido[4,3-b]pyridinyl, pyrido[2,3-b]pyridinyl, 1,3,2-benzozazinyl, 1,4,2-benzoxazinyl, 2,3,1-benzoxazinyl, 3,1,4-benzoxazinyl, 1,2-benzisoxazinyl, 1,4-benzisoxazinyl, carbazolyl, purinyl, and partially saturated heterocyclic radicals selected from the list above. All of the preferred heterocyclic radicals contain at least one double bond. When the heterocyclic radical is partially saturated, one or more of the olefins in the unsaturated ring system is saturated; the partially saturated heterocyclic radical still contains at least one double bond. It is more preferred that hetaryl is pyridinyl.

For the amidino carbamates having structure II, it is preferred that the



moieties are pyrrolyl, 3,4-dihydropyrrolyl, pyrolidinyl, pyrazolyl, imidazolyl, 4,5-dihydroimidazolyl, 2-pyrazolinyl, 1,2,4-triazolyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, pyridinyl, 1,2,3,6-tetrahydropyridinyl, piperidinyl, pyridazinyl, pyrimidinyl, 1,4,5,6-tetrahydropyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, hexahydro-1,3,5-triazinyl, 1,2,4-triazinyl, 1,3,2-oxazinyl, 1,4-oxazinyl, morpholinyl, azepinyl, indolyl, indolinyl, indolenyl, benzoxazolyl, quinolinyl, 1,2,3,4-tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinolinyl, isoquinolinyl, 3,4-dihydroisoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, and, 5,6,7,8-tetrahydroisoquinolinyl radicals that are optionally substituted by $R^8$. The fourth ring structure, above, is the more preferred of the four ring systems, and within this ring system it is more preferred that the radical is 4,5-dihydroimidazolyl or 1,4,5,6-tetrahydropyrimidinyl. It is also preferred that the $R^7$ substituent, when present, is phenyl.

The compounds of this invention carbamylated at the 42-position or at both the 31- and 42-positions can be prepared by converting the 42- and/or 31-alcohols of rapamycin to a carbonate (see Example 1 ) followed by reaction with an appropriately substituted amine to provide the desired carbamate. The following scheme illustrates the preparation of the compound of Example 4.



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