US007091213B2

(12) **United States Patent**
Metcalf, III et al.

(10) **Patent No.: US 7,091,213 B2**
(45) **Date of Patent: Aug. 15, 2006**

(54) **PHOSPHORUS-CONTAINING COMPOUNDS AND USES THEREOF**

(75) Inventors: **Chester A. Metcalf, III**, Needham, MA (US); **Leonard W. Rozamus**, Bedford, MA (US); **Yihan Wang**, Newton, MA (US); **David L. Berstein**, Waban, MA (US)

(73) Assignee: **ARIAD Gene Therapeutics, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/862,149**

(22) Filed: **Jun. 4, 2004**

(65) **Prior Publication Data**

US 2005/0032825 A1 Feb. 10, 2005

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/635,054, filed on Aug. 6, 2003, now abandoned, and a continuation-in-part of application No. 10/357,152, filed on Feb. 3, 2003, now abandoned.

(60) Provisional application No. 60/433,930, filed on Dec. 17, 2002, provisional application No. 60/428,383, filed on Nov. 22, 2002, provisional application No. 60/426,928, filed on Nov. 15, 2002, provisional application No. 60/353,252, filed on Feb. 1, 2002.

(51) **Int. Cl.**

C07D 491/06	(2006.01)
A61K 31/395	(2006.01)
A61P 35/00	(2006.01)
A61P 35/02	(2006.01)

(52) **U.S. Cl.** **514/291**; 540/456

(58) **Field of Classification Search** 540/456; 514/291

See application file for complete search history.

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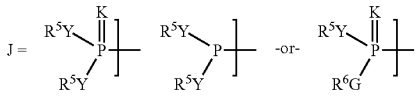
Primary Examiner—Bruck Kifle
(74) *Attorney, Agent, or Firm*—David L. Berstein

(57) **ABSTRACT**

This invention concerns a new family of phosphorus-containing compounds containing a moiety JQA- in which:
A is absent or is —O—, —S— or —NR^2—;
Q is absent or (if A is —O—, —S— or —NR^2—) Q may be —V—, —OV—, —SV—, or —NR^2V—, where V is an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, such that J is linked to the cyclohexyl ring directly, through A or through VA, OVA, SVA or NR^2VA;



K is O or S;
each occurrence of Y is independently —O—, —S—, —NR^2—, or a bond linking a R^5 moiety to P;
each occurrence of R^2 and R^5 is independently an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, or H; and
each occurrence of R^6 is independently —PK(YR^5)(YR^5), —SO_2(YR^5) or —C(O)(YR^5); so long as any R^2, or R^5 moiety linked directly to P is not H;
wherein two R^2, R^5 and/or R^6 moieties may be chemically linked to one another to form a ring;
each occurrence of G is independently —O—, —S—, —NR^2— or $(M)_x$;
each occurrence of M is independently a substituted or unsubstituted methylene moiety, and any M-M' moiety may be saturated or unsaturated;
each occurrence of x is independently an integer from 1–6; and the other variables are as defined herein.

36 Claims, No Drawings

PHOSPHORUS-CONTAINING COMPOUNDS AND USES THEREOF

RELATED APPLICATIONS

The present application is a continuation-in-part of U.S. patent application Ser. No. 10/635,054, filed Aug. 6, 2003 now abandoned and U.S. patent application Ser. No. 10/357,152, filed Feb. 3, 2003 now abandoned and claims priority thereto and under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 60/353,252, filed Feb. 1, 2002, U.S. Provisional Patent Application No. 60/426,928, filed Nov. 15, 2002, U.S. Provisional Patent Application No. 60/428,383, filed Nov. 22, 2002, and U.S. Provisional Patent Application No. 60/433,930, filed Dec. 17, 2002, the entire contents of each of these applications are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Rapamycin is a macrolide antibiotic produced by *Streptomyces hygroscopicus*. It binds to a FK506-binding protein, FKBP12, with high affinity to form a rapamycin:FKBP complex. Reported Kd values for that interaction are as low as 200 pM. The rapamycin:FKBP complex binds with high affinity to the large cellular protein, FRAP, to form a tripartite, [FKBP:rapamycin]:[FRAP], complex. In that complex rapamycin can be viewed as a dimerizer or adapter to join FKBP to FRAP. Formation of the complex is associated with rapamycin's various biological activities.

Rapamycin is a potent immunosuppressive agent and is used clinically to prevent rejection of transplanted organs. Rapamycin and/or its analogs, CCI 779 (Wyeth) and SDZ Rad ("RAD001", Novartis) are promising agents for treating certain cancers, for immune suppression and/or for helping to decrease the incidence of restenosis following interventional cardiology. Rapamycin has also been shown to have activity as an antifungal agent, in the experimental allergic encephalomyelitis model (a model for multiple sclerosis), in the adjuvant arthritis model (for rheumatoid arthritis), in inhibiting the formation of IgE-like antibodies, and for treating or preventing lupus erythematosus, pulmonary inflammation, insulin dependent diabetes mellitus, adult T-cell leukemia/lymphoma, and smooth muscle cell proliferation and intimal thickening following vascular injury. See e.g. U.S. Pat. appln 2001/0010920.

Because it serves as an adapter to complex FKBP with FRAP, rapamycin is also capable of multimerizing appropriately designed chimeric proteins incorporating domains derived from FKBP and FRAP, respectively; Because of that activity, rapamycin and various derivatives or analogs thereof have also been used as multimerizing agents for activating biological switches based on such chimeric proteins. See e.g., WO96/41865; WO 99/36553; WO 01/14387; Rivera et al, Proc Natl Acad Sci USA 96, 8657–8662; and Ye, X. et al (1999) Science 283, 88–91.

Rapamycin's potential for providing relief from such an important swath of cruel diseases has stimulated the search for rapamycin analogs with improved therapeutic index, pharmacokinetics, formulatability, ease or economy of production, etc. The resulting investigation by the pharmaceutical industry and academic researchers has been a sustained one over the past few decades. This has led to the exploration of materials and methods for effecting chemical transformations of rapamycin, including reductions of ketones, demethylations, epimerizations, various acylations and alkylations of hydroxyls, etc.

A large number of structural variants of rapamycin have now been reported, typically arising as alternative fermentation products and/or from synthetic efforts. For example, the extensive literature on analogs, homologs, derivatives and other compounds related structurally to rapamycin ("rapalogs") include, among others, variants of rapamycin having one or more of the following modifications relative to rapamycin: demethylation, elimination or replacement of the methoxy at C7, C42 and/or C29; elimination, derivatization or replacement of the hydroxy at C13, C43 and/or C28; reduction, elimination or derivatization of the ketone at C14, C24 and/or C30; replacement of the 6-membered pipecolate ring with a 5-membered prolyl ring; and alternative substitution on the cyclohexyl ring or replacement of the cyclohexyl ring with a substituted cyclopentyl ring. Additional historical information is presented in the background sections of U.S. Pat. Nos. 5,525,610; 5,310,903 and 5,362,718. See also U.S. Pat. No. 5,527,907. Materials and methods have even been developed for the remarkably effective and selective epimerization of the C-28 hydroxyl group (WO 01/14387).

New rapalogs with reduced immunosuppressive activity and/or interesting pharmacokinetic or bioavailability profiles would be very desirable for use as multimerizing agents or antifungal agents.

New rapalogs with attractive physicochemical or functional characteristics, e.g., in therapeutic index, bioavailability, pharmacokinetics, stability, etc., would also be of interest for a variety of pharmaceutical uses such as are mentioned above, including among others use as immunosuppressants, as anticancer agents and in reducing the incidence of restenosis following interventional cardiology (e.g. on drug-bearing stents).

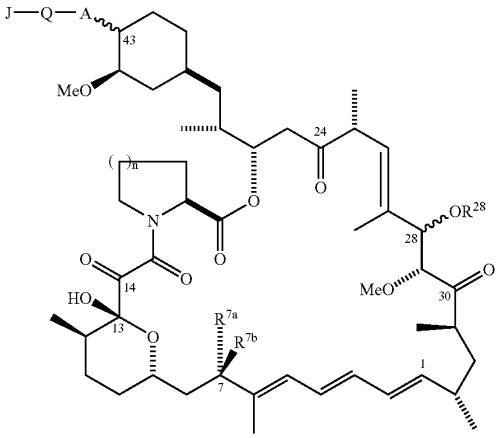
The only rapalogs thought to be in clinical development as immunosuppressants at present are those with rather modest, conventional structural modifications, i.e., acylation or alkylation at C-43 (CCI 779 and SDZ RAD, respectively; see e.g., Yu, K. et al., Endocrine-Related Cancer (2001) 8, 249–258; Geoerger, B. et al., Cancer Res. (2001) 61 1527–1532) and Dancey, Hematol Oncol Clin N Am 16 (2002):1101–1114. Stents bearing a tetrazole-substituted rapalog, ABT-578, but having only a shortened biological half-life (see e.g. WO 03/022807 and 99/15530) are reportedly being studied too.

The invention described below represents a rather dramatic departure in the design of new rapalogs based on the incorporation of a phosphorus-containing moiety.

SUMMARY OF THE INVENTION

Compounds of this invention include a new family of compounds of Formula (1):

I

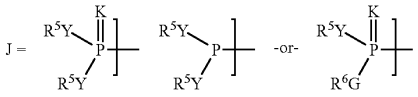


and pharmaceutically acceptable derivatives thereof. Compositions containing such compounds and uses thereof are also provided.

In the compounds of this invention,

A is —O—, —S— or —NR^2—, or is absent (i.e., is a covalent bond linking JQ- to carbon 43);

Q is absent (i.e., is a covalent bond linking J to A or to carbon 43) or, if A is —O—, —S— or —NR^2—, Q may be —V—, —OV—, —SV—, or —NR^2V—, where V is an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, such that J is linked to the cyclohexyl ring directly, through A or through VA, OVA, SVA or NR^2VA (i.e., as JA-, JVA-, JOVA-, JSVA- and JNR^2VA-;



K is O or S;

each occurrence of Y is independently —O—, —S—, —NR^2—, or a chemical bond linking a R^5 moiety to P;

each occurrence of R^2 and R^5 is independently an aliphatic, heteroaliphatic, aryl, or heteroaryl moiety, or H; and each occurrence of R^6 is independently —PK(YR^5)(YR^5), —SO_2(YR^5) or —C(O)(YR^5); so long as any R^2 or R^5 moiety linked directly to P is not H (e.g., —PR^2 and —PR^5 cannot be —PH);

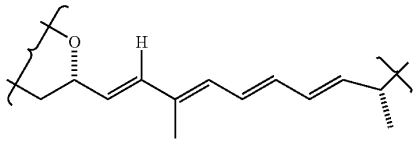
wherein two R^2, R^5 and/or R^6 moieties may be chemically linked to one another to form a ring;

each occurrence of G is independently —O—, —S—, —NR^2— or $(M)_x$;

each occurrence of M is independently a substituted or unsubstituted methylene moiety, and any M-M' moiety may be saturated or unsaturated;

each occurrence of x is independently an integer from 1–6;

one of R^{7a} and R^{7b} is H and the other is H, halo, —R^A, —OR^A, —SR^A, —OC(O)R^A, —OC(O)NR^AR^B, —NR^AR^B, —$NR^BC(O)R^A$, —$NR^BC(O)OR^A$, —NR^BSO2R^A or —$NR^BSO2NR^AR^B$; or R^{7a} and R^{7b}, taken together, are H in the tetraene moiety:



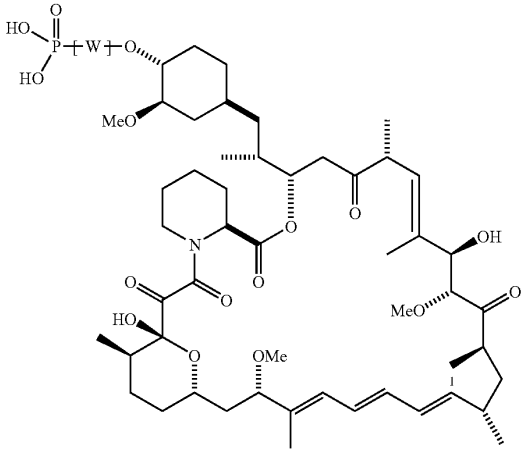
where R^A is R^2 and where R^B is OH or R^2. In some cases one or both of R^A and R^B is H;

R^{28} is hydrogen; J; or an aliphatic, heteroaliphatic, aryl, heteroaryl, acyl, aroyl or heteroaroyl moiety;

and n is 1 or 2;

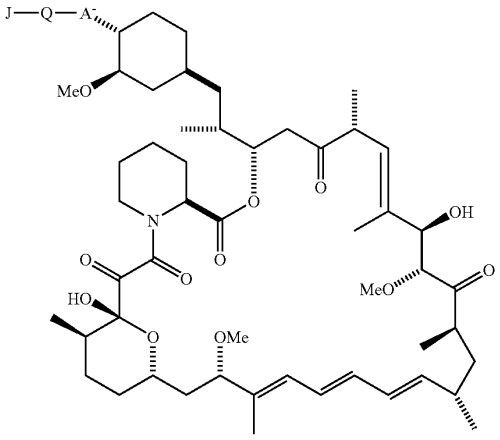
wherein each of the foregoing aliphatic and heteroaliphatic moieties is independently linear or branched, or cyclic or acyclic, and substituted or unsubstituted, and each of the aryl, heteoraryl, acyl, aroyl or heteroaroyl moieties is independently substituted or unsubstituted;

with the proviso that (a) if JQA- is (R^2Y)(Me)(P═O)O—, then (R^2Y) is (i) not an immunogenic carrier material, detector carrier material or a solid matrix, or (ii) R^2 contains 15 or fewer carbon atoms, preferably 10 or fewer); and (b) the compound is not



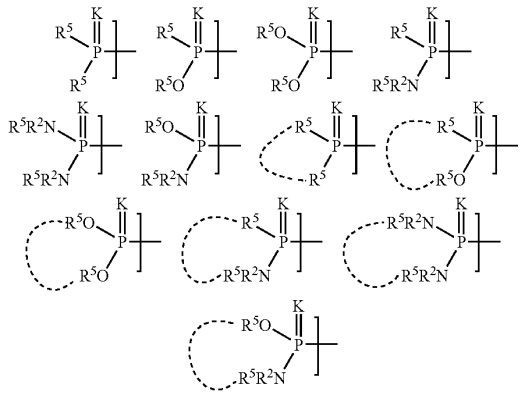
or a desmethyl or reduced analog thereof, or a salt of any of the foregoing, where W comprises a substituted or unsubstituted heterocycle comprising

alone or fused to a six-membered aromatic ring, wherein U is substituted or unsubstituted amino, O, S, SO or SO_2; and (c) in compounds of the formula:

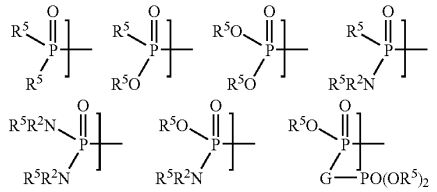


J-Q-A- is not $(HO)_2(PO)$—O— or the dimethyl phosphate ester thereof (and preferably not another di-lower alkyl ester thereof). Wavy bonds, e.g., as shown in FIG. 1 at positions 28 and 43 indicate that the substituent may be in either orientation.

J moieties of special interest in various embodiments of this invention include those shown in Series 1:



where K, R^2, R^5 and R^6 are as defined above. J moieties currently of special interest are those in which K is oxygen, as are illustrated in numerous exemplary compounds depicted below, including among others, any of the following:

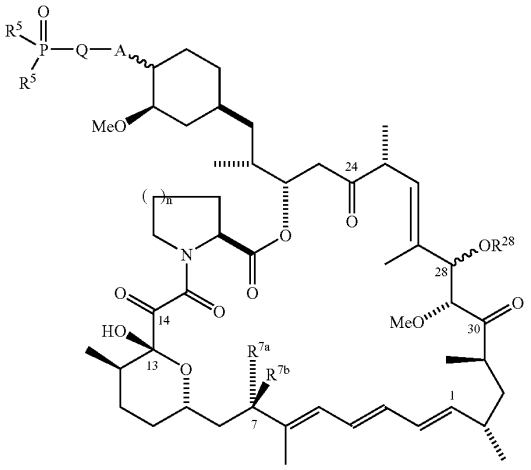


in which each occurrence of R^5 is an independently chosen lower aliphatic or aryl moiety, which may be substituted or unsubstituted, or in the case of —OR^5 moieties, may alternatively be H. Also of current special interest are embodiments in which -Q-A- is O, especially in cases in which J is one of the currently preferred J moieties noted just above (although preferably not —PO_3H_2). Of special interest too are any of the foregoing compounds in which in which JQA- is $(R^2Y)(Me)(P{=}O)O$— in which R^2Y— contains 15 or fewer carbon atoms, preferably 10 or fewer carbon atoms, and in some embodiments 6 or fewer carbon atoms.

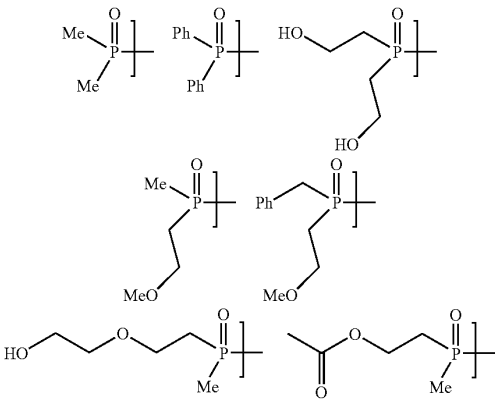
This new family of compounds includes a number of classes of compounds of particular interest.

For instance, one such class is illustrated by formula (a):

(a)



In this class, each R^5 is an independently selected, aliphatic, heteroaliphatic, aryl, or heteroaryl moiety (which moiety may be substituted or unsubstituted), especially a lower (i.e. from 1 to 6 carbons) aliphatic moiety, e.g., a lower alkyl, which may be optionally substituted (e.g. with a halo, hydroxyl, —O-acyl (i.e., acyloxy), alkoxyl, haloalkyl-, hydroxyalkoxyl, aryl, or heteroaryl moiety, etc.). In several examples of this class, the compounds of formula (a) comprise a moiety, J, selected from the following:



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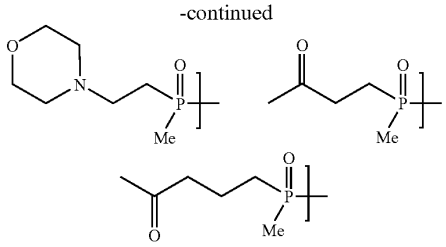
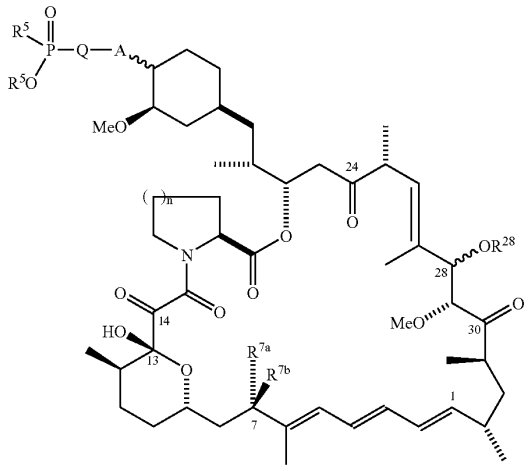


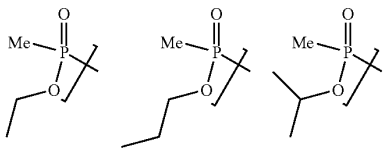
This class is further illustrated in the synthetic examples that follow, through members of its subclass in which J-Q-A- is $(R^5)_2PO—O—$. Furthermore, note that all of the R^2, R^5, R^6 and J moieties disclosed or exemplified herein in connection with a given compound, subclass or class of compounds are equally applicable in other cases unless otherwise specified. Thus, the disclosure of a R^2, R^5, R^6 or J moiety in one case is intended to be extrapolated to all other cases except as otherwise noted.

Another class of compounds of this invention which is also of interest is illustrated by formula (b):

(b)



In this class, each R^5 is an independently selected, aliphatic, heteroaliphatic, aryl, or heteroaryl moiety (which moiety may be substituted or unsubstituted), especially a lower aliphatic moiety, e.g. a lower alkyl, which may be optionally substituted (e.g. with a hydroxyl, alkoxyl, hydroxyalkoxyl, acyloxy-, aryl, or heteroaryl moiety, etc.). In the case of —OR^5, the R^5 moiety may additionally be H. Illustrative examples include compounds of formula (b) in which J is selected from the following:



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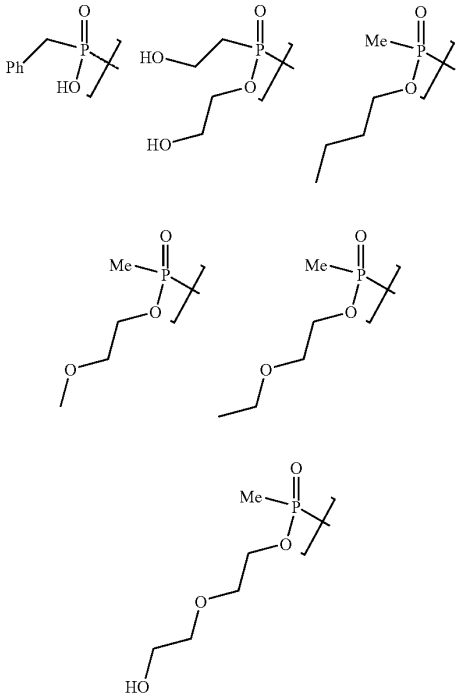
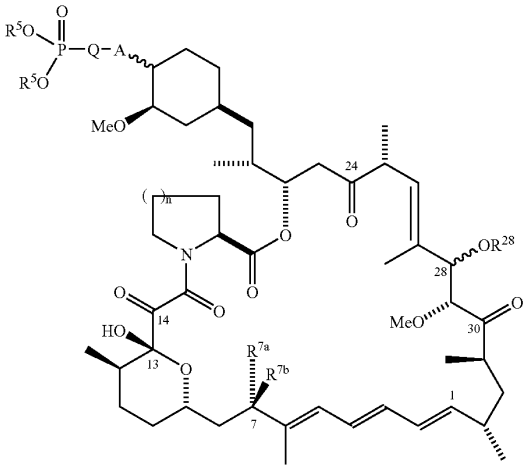


This class is further illustrated in the synthetic examples that follow, through members of its subclass in which J-Q-A- is $(R^5)(R^5O)PO—O—$.

Another class of compounds of this invention which is also of interest is illustrated by formula (c), with the proviso noted at the outset:

(c)



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