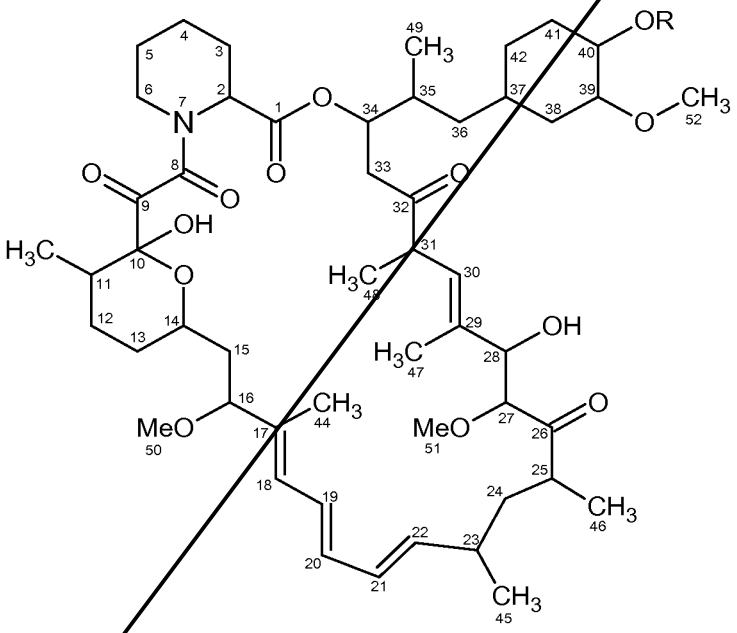
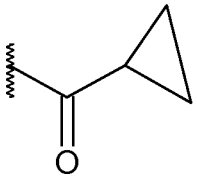
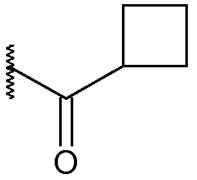
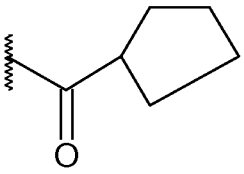
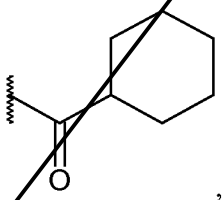
To reduce the rate of restenosis in a PTCA procedure, the stent may be coated with rapamycin or a rapamycin derivative in a form that allows slow release of the drug from the stent against the endothelial cells of the vessel, typically over a two-week to several-month interval. The stent coating may consist of a polymer, e.g., bioerodable polymer, with encapsulated drug, or the drug itself may form a cohesive coating. In either case, the coating may be susceptible to cracking as the stent is expanded at the implantation site, and any loose pieces of coating that break off can be a significant clotting hazard in the bloodstream. Another problem that has been observed heretofore in rapamycin stents is relatively poor drug stability, as evidence by mass balance measurement on the amounts of active drug released from the stent coatings, typically showing less than 40% of active drug recovered after elution from the stent.

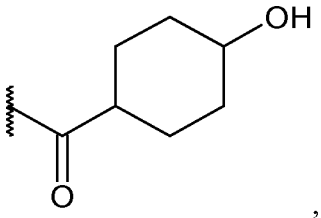
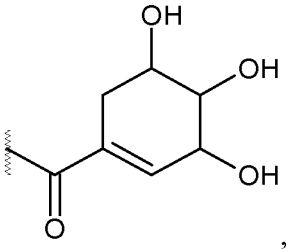
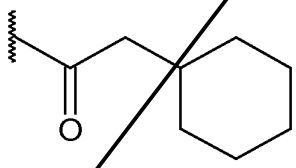
In one aspect, the invention includes a rapamycin 40-O-cyclic hydrocarbon ester having the structure:



where R is $C(O)-(CH_2)_n-X$, n is 0, 1 or 2, X is a cyclic hydrocarbon having 3-8 carbons, optionally containing one or more unsaturated bonds, one or more linear-chain or cyclic carbon atoms may contain an OH or halide substitution, and the rapamycin parent structure may contain substitutions at other positions.

Exemplary R groups include:

 ,  ,  ,  ,

 ,  , and 

In another aspect, the invention includes a method of treating any of the following conditions in a mammal: (i) restenosis; (ii) wound healing; (iii) vascular injury; (iv) vascular inflammation; (v) transplantation rejection; (vi) proliferative ophthalmic diseases, including wet age-related macular degeneration (AMD) and diabetic macular edema (DME); (vii) uveitis; (viii) cancer; (ix) various skin conditions such asatopic dermatitis, eczema, tuberous sclerosis, neurofibromatosis, lichen planus and the like; (x) ear-nose-throat treatments such as sinusitis treatment with sinus stents or balloons by administering to the mammal, a therapeutic amount of the rapamycin 40-O-cyclic hydrocarbon ester. For inhibiting restenosis at a vascular injury site, the rapamycin ester may be administered from a drug-eluting stent placed at the vascular injury site.

Also disclosed is a drug-eluting stent having an expandable stent body formed of one or more filaments and carried on the one or more filaments, a coating containing the above rapamycin 40-O-cyclic hydrocarbon ester. The coating may be formed of the rapamycin compound alone, or formed of a polymer, e.g., bioerodable polymer such as polylactic acid, containing the rapamycin ester in entrapped form. Other suitable polymers include poly(caprolactone), poly(trimethylene carbonate), polyester amide, poly(glycolide), polyhydroxyalkanoates including poly(hydroxyvalerate), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polyorthoester, polyanhydride, poly(glycolic acid). The

stent is used in a method for inhibiting restenosis at the site of vascular injury, by placing the stent at the site of vascular injury.

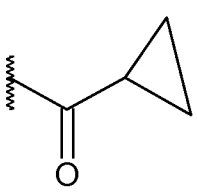
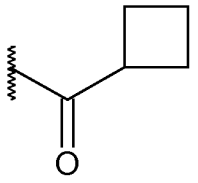
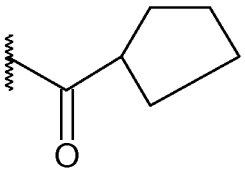
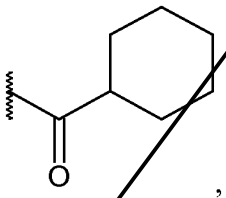
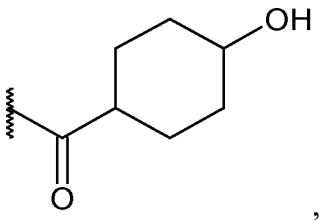
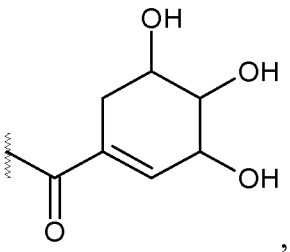
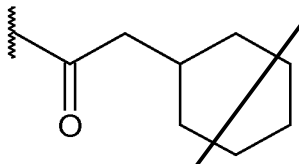
Further disclosed are pharmaceutical compositions, including microparticle compositions, such as liposomes and bioerodable polymer particle compositions, containing the rapamycin ester in an encapsulated or captured form for release over time from a site of administration or implantation of the composition. Microparticles containing the rapamycin analog may be inherently porous with pore sizes ranging from about 5 nanometers to about 10 microns in diameter.

In still another embodiment, the invention includes an improvement in an intravascular stent of the type having an expandable stent body formed of one or more filaments, such as a metal-filament stent, and carried on the one or more filaments, a polymer coating containing 40%-80% polymer, such as a bioerodable polymer, and 20% to 60% rapamycin compound having a 40-position -OH or $-O(CH)_nOH$ substituent, where n=1 to 5. The improvement, which significantly reduces the tendency of the coating to flake or crack when the stent body is expanded, includes substituting in the rapamycin compound, the rapamycin 40-O-cyclic hydrocarbon ester of the invention.

These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying figures.

Fig. 1 shows the effects of stent expansion on a polymer coating containing 50 weight percent rapamycin on the stent filaments;

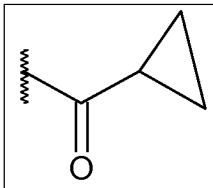
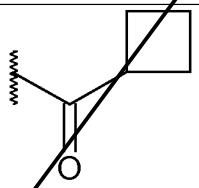
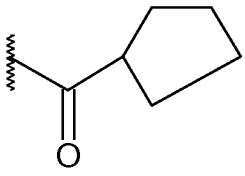
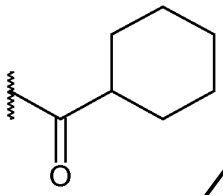
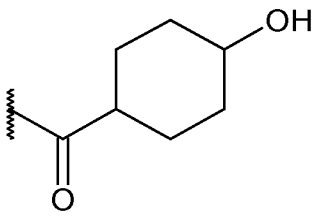
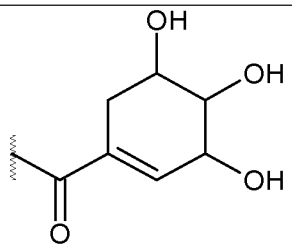
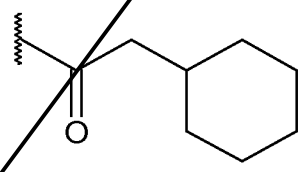
Fig. 2 shows the effects of stent expansion on a polymer coating containing 50 weight percent rapamycin 40-O-cyclic hydrocarbon ester in accordance with one aspect of the invention.


,

,

,

,

,

, and


II. Synthesis of rapamycin 40-O-cyclic hydrocarbon esters

Table I below shows the R group for a number of exemplary analogs formed in accordance with the present invention.

Table I

 **1**	 **2**	 **3**
 **4**	 **5**	 **6**
 **7**		

IIG. Rapamycin 40-O-Cyclic Hydrocarbon Ester with Cyclohexaneacetyl Chloride (Compound 7)

Compound 7 was prepared by dissolving 20 mg rapamycin in 100 µL methylene chloride contained in a 1.5-mL HPLC glass vial with stirring bar and capped. With stirring, 3 µL pyridine was added and followed with 10µL cyclohexaneacetyl chloride, as received. The reaction vessel was placed at ambient temperature and reaction continued with stirring for 1 hour.

The product was analyzed by High Resolution LCMS. Table VIII compares the exact mass calculated and exact mass found for the title compound ($C_{59}H_{91}NO_{14}$) with Na^+ adduct.

Table VIII

$C_{59}H_{91}NO_{14}Na$	
Exact Mass Calculated	1060.6337
Exact Mass Found	1060.6337

III. Compound Properties

IIIA. Increased ductility of a coating formed from the analog

The 40-O-cyclic hydrocarbon rapamycin esters of the invention are designed for use in a variety of therapeutic uses, as detailed in Section IV below. One of the important uses is for slow-release of the drug from a stent coating in treating/preventing restenosis following percutaneous transluminal coronary angioplasty (PTCA). In this procedure, the coated stent is delivered to the site of vascular injury in a contracted, low-diameter condition in a balloon catheter, and then expanded to the dimensions of the treated vessel at the site. In this application, it is important that the drug coating is sufficiently ductile that it does not crack or flake off the outer stent surface during stent expansion, since loose pieces of coating, if released into the bloodstream, may present a serious clotting hazard.

In accordance with one of the unexpected advantages of the present invention, it has been discovered that a coating formed with the compounds of the present invention is substantially more ductile, i.e., less prone to cracking, than a coating formed with rapamycin. This property can be seen from the photomicrographs of Figs. 1 and 2, which show the condition of a stent coating after stent expansion in a stent formed of a 1:1 weight ratio of a 40-O-cyclic hydrocarbon rapamycin ester and polylactic acid (Fig. 1) and a coating formed of a 1:1 weight ratio of Compound 1 (Table I) and polylactic acid (Fig. 2). As seen, the drug compound of the present invention provides for a coating that is more ductile, and more resistant to delamination and particle shedding and in general, appears to function as a plasticizer for the polylactate coating. An important advantage of the drug compound in this setting is that a coating with a high drug:polymer ratio can be prepared without the need for addition of a separate plasticizer, which may cause toxic responses, affect drug elution rates, and extend development times and increase production costs.

In one aspect, the invention includes an improvement in an intravascular stent of the type having an expandable stent body formed of one or more filaments, such as a metal-filament stent, and carried thereon, a drug-eluting polymer coating containing 40-80 weight percent polymer and 20 to 60 weight percent of a rapamycin compound having a 40-O-H or 40-O-linear alcohol group. The improvement, which significantly reduces the tendency of the coating to flake or crack when the stent body is expanded, includes substituting for the rapamycin compound, the rapamycin 40-O-cyclic hydrocarbon ester of the present invention.

IIIB. Drug Elution and Stability

This section examines the stability of the compounds of the invention when released from a reservoir over a several-day to several-week period. In one study, a series of stents were prepared with a suitable coating of drug/ polymer mixture. The stents were fabricated from laser cut and electropolished 316L Stainless Steel and measured 16millimeters in length. The coating mixture contained an equal weight of polylactic acid and each of the compounds to be evaluated. The mixture components were weighed, combined in a glass vial with acetone at room temperature and then vortexed until all of the materials

HPLC as above. The amount of drug recovered at each time point and the exhaustive extraction was summed for each stent to determine the total amount of drug recovered, and the results for rapamycin and a rapamycin 40-O-cyclic hydrocarbon ester are shown in the table below.

	Stent #	**Drug Amount (µg)**	**Total Drug (µg) Recovered**	**% Recovery**
Rapamycin	1	238	84.6	35.6
	2	238	103.4	43.4
	3	236	125.2	53.1
	4	236	71.6	32.8
	5	241	109.1	45.3
Average				**42.0**
Standard Deviation				**8.1**
Rapamycin 40-Cyclic Hydrocarbon Ester	6	228	192.5	84.6
	7	233	202.2	87.0
	8	233	198.7	85.3
	9	236	202.4	85.8
	10	241	197.8	82.2
Average				**85.0**
Standard Deviation				**1.8**

Average % recovery for rapamycin and the rapamycin 40-cyclic hydrocarbon ester were 42.0±8.1 and 85.0±1.8, respectively. This indicates that, unexpectedly, drug compounds of the present invention are more stable than rapamycin during elution conditions. This property is important as it allows for a lower drug dose to be utilized for patient treatment and also is beneficial for the drug product regulatory approval and quality control purposes because a high in vitro elution recovery is taken as evidence that the drug substance is stable, the test procedure is an accurate monitor of manufacturing quality and good drug product performance can be maintained.

IIIC. Inhibition of Restenosis

Trial A

Stainless steel coronary artery stents coated with the rapamycin 40-O-cyclic hydrocarbon ester of the invention were compared for their ability to control induced restenosis using a 28 day porcine arterial over stretch model. Four different groups of stents were evaluated with the drug compound and in different coating configurations. Group 1 consisted of five stainless steel stents which were first coated with a base layer consisting of a copolymer of polycaprolactone and poly L lactic acid. A topcoat of poly d,l lactic acid and 225 micrograms of rapamycin 40-O- cyclic hydrocarbon ester was then applied. Group 2 consisted of five stainless steel stents with the same base coat and a topcoat of poly d,l lactic acid and 100 micrograms rapamycin 40-O-cyclic hydrocarbon ester. Group 3 consisted of five stents with a drug topcoat consisting only of 100 micrograms of rapamycin 40-O-cyclic hydrocarbon ester applied directly to a base coat of the polycaprolactone-poly L lactic acid copolymer. Finally, Group 4 consisted of five stents with a base coat of parylene polymer and a topcoat of poly d,l lactic acid and 225 micrograms of rapamycin 40-O-cyclic hydrocarbon ester. All of the stents were 16 millimeters in length and were mounted on standard balloon delivery systems and were then sterilized with ethylene oxide gas. The balloon to artery ratio of the deployed stents was approximately 1.20 : 1.00. The matrix of coating layers and drug dosages was chosen with the intent to optimize the adhesion of the active drug compound to the stent surface and to determine the best means to transfer the drug to the surrounding vessel wall upon stent deployment.

The primary objective of this study was to evaluate the drug compound coating on stents to treat vessels in which injury was intentionally induced. Coronary artery measurements were made from angiographic images before stent deployment, immediately after deployment, and twenty-eight days after deployment to determine the effectiveness of the coated stent in reducing restenosis. Determination of angiographic late loss was made by subtraction of the minimum vessel lumen diameter of the stented vessel at 28 days post-

IV. Compositions and Applications

IVA. Compositions

In another aspect, the invention includes a composition incorporating the rapamycin 40-O-cyclic hydrocarbon rapamycin ester of the invention, where the composition serves a drug reservoir for release, typically in a controlled fashion, of the compound into a treatment site.

Micro and Macro Particles

One exemplary composition includes a suspension of polymer particles that can be introduced into a suitable treatment site *in vivo* via injection or delivery through a catheter. The polymer particles can be microporous, macroporous, or non-porous and can be formed of a polymer that acts as a suitable drug reservoir. Exemplary polymer particles are described, for example, in U.S. Pat. No. 5,135,740, incorporated by reference herein. Liposomal particles that incorporate the compound in encapsulated or membrane-entrapped form are also contemplated. Polymers suitable for particle formation include, but aren't limited to poly(d, l-lactic acid), poly(l-lactic acid), poly(d-lactic acid), poly (glycolic acid) and copolymers and mixtures of polylactate and polyglycolic. Other suitable polymers include methacrylate polymers, such as polybutyl methacrylate, ethylene vinyl alcohol (EVOH), .epsilon.-caprolactone, glycolide, ethylvinyl hydroxylated acetate (EVA), polyvinyl alcohol (PVA), polyethylene oxides (PEO), polyester amides, and co-polymers thereof and mixtures thereof. Typically, the composition is formulated to contain between 20-80 weight percent polymer and 20-80 weight percent rapamycin compound. An exemplary formulation contains between 20 and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight percent of a polylactate or polyglycolate polymer or a polylactate/polyglycolate copolymer or mixed polymer. The particles have typical sizes between about 0.1 micron to about 100 microns in diameter, preferably from about 0.5 microns to about 20 microns, and can be administered as liquid, paste, or gel suspension.

Drug-Coated Stent

In another general embodiment, the invention includes an endovascular stent coated with the drug alone or the drug formulated in a polymer coated, such as the drug-polymer formulations described above. Such stents are typically cylindrical, expandable metal-frame structures whose struts or filaments may be coated, on their outer surfaces, with a drug-eluting coating. When placed in a body lumen, a stent is expanded to press against the wall of the vessel and hold the stent in place, while drug is eluted from the stent against the wall of the vessel.

An exemplary coating contains equal amounts by weight of compound 1 and d,l PLA material, which may be formulated and applied to the stent outer surface according to well known methods. An example stent product is described in US patent 7,214,759 where polymers containing polyesters and optional therapeutic agents are applied to implantable substrates, including stents. Coatings applied to the surface of stents may incorporate excipient materials along with the rapamycin 40 O-cyclic hydrocarbon esters which enhance the adhesion properties or elution profile of the drug, or impart other beneficial properties to the system. The coating may contain or be composed of micro or macroporous drug reservoirs. The coating may be comprised of the drug compound alone. Those familiar with the art are aware that these examples do not limit the scope of the invention.

IVB. Treating restenosis: compound delivery from a catheter balloon

In another vascular application, rapamycin 40 O-cyclic hydrocarbon esters can be applied as a coating to the surface of the inflatable balloon portion of a percutaneous vascular angioplasty balloon catheter in a manner that when the balloon is placed adjacent to a vascular target lesion and then inflated the drug will separate from the balloon surface and transfer to the affected tissue. In this method of drug delivery the balloon distributes the drug homogenously along the arterial wall, whereas in drug-eluting stents the highest concentration is under the wire components of the stents. Whereas stents generally permanently alter the vessel wall the drug coated balloon is removed after deployment, leaving only the remaining drug and coating. In US patent 7,572,245 Herweck, et al.

describe a means to deliver a therapeutic agent a vessel lumen by positioning a coated balloon within a target vessel and through inflation of the balloon atraumatically smearing the coating agent against the vascular lesion, thus transferring a portion through lipophilic absorptive action. In US patent 7,750,041 Speck, et al. reveal an angiography catheter comprising a coating of paclitaxel and iopromide applied to the balloon portion of the catheter which is released to surrounding tissue upon balloon inflation.

Coatings applied to the surface of vascular balloons may incorporate excipient materials along with the rapamycin 40 O-cyclic hydrocarbon esters which enhance the adhesion properties or elution profile of the drug, or impart other beneficial properties to the system. The coating may contain or be composed of micro or macroporous drug reservoirs. The coating may be comprised of the drug compound alone.

IVC. Treating Ocular Disorders

Compounds in the subject invention may be used to treat ocular disosorders. Rapamycin itself has been evaluated clinically for treatment of macular degeneration. In clinical trials subconjunctival injections of rapamycin in doses ranging from 220 micrograms to 880 micrograms to verify increased visual acuity in a 180 day timeframe. Rapamycin has also been applied systemically in conjunction with corticosteroids for treatment of non-infectious uveitis. The compounds of the subject can be utilized in valved or non-valved stents/shunts used for glaucoma drainage In the present invention, the ocular disorders are treated by administering to a mammalian subject in need of treatment, a therapeutic amount of the rapamycin alkyl ester analog of the present invention.

IVD. Treating Cancers

Compounds in the subject invention are also useful in the treatment of cancer. Rapamycin itself is currently in clinical pancreatic cancer trials as well as skin cancer trials and breast cancer trials. The therapeutic effect of rapamycin and related compounds in cancer and malignant tumor treatment is likely caused by disruption of the biochemical pathways involved in the development of new blood vessels. Rapamycin when combined with cancer

drug Carboplatin have also been found to potentially improve the efficiency of ovarian cancer treatment. Rapamycin has also been shown to inhibit the progression of dermal Kaposi's sarcoma. Other mTOR inhibitors, such as temsirolimus and everolimus are currently being tested for use in cancers such as glioblastoma multiforme and mantle cell lymphoma. In the present invention, a cancer is treated by administereing to a mammalian subject in need of treatment, a therapeutic amount of the rapamycin 40-O-cyclic hydrocarbon ester analog of the present invention.

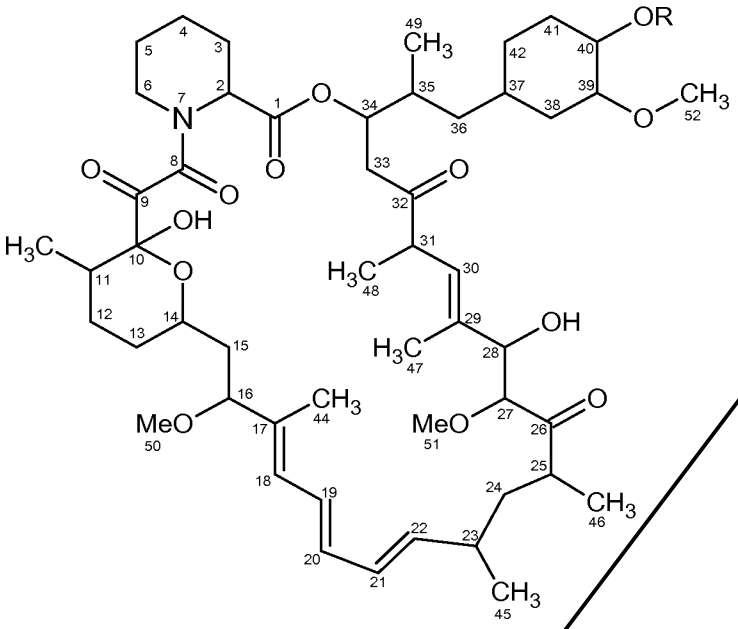
IVE. Prevention of Transplant Rejection

Rapamycin and its analogs can be used alone, or in conjunction with calcineurin inhibitors, such as tacrolimus to provide immunosuppression regimens. Transplant patients can be given oral medications which include rapamycin under the trade name Rapamune® or everolimus, a rapamycin analog under the trade name Certican® to reduce the incidence of tissue rejection. These therapies have the advantage of having lower toxicity toward kidneys. In the present invention, the subject is treated by administering a therapeutic amount of the rapamycin alkyl ester analog of the present invention.

Although the invention has been described with respect to particular embodiments and applictions, it will be appreciated that various additional modification the applications may be made consistent with the scope of the claims.

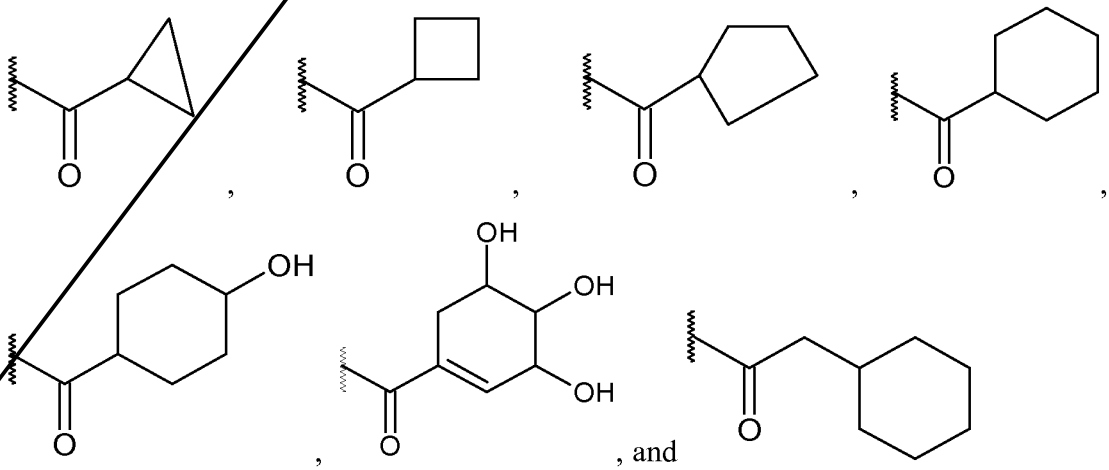
PATENT CLAIMS

1. A rapamycin 40-O-cyclic hydrocarbon ester compound having the structure:



where R is $C(O)-(CH_2)_n-X$, n is 0, 1 or 2, X is a cyclic hydrocarbon having 3-8 carbons, optionally containing one or more unsaturated bonds, one or more linear-chain or cyclic carbon atoms may contain an OH or halide substitution, and the rapamycin parent structure may contain substitutions at non-40 positions.

2. The compound of claim 1, wherein $C(O)-(CH_2)_n-X$ has one of the structures:



, and

3. A method of treating (i) restenosis; (ii) wound healing; (iii) vascular injury; (iv) vascular inflammation; (v) transplantation rejection; (vi) proliferative ophthalmic diseases, including wet age-related macular degeneration (AMD) and diabetic macular edema (DME); (vii) uveitis, or (viii) cancer in a mammal, by administering to the mammal, a therapeutic amount of the rapamycin 40-O-cyclic hydrocarbon ester of claim 1.

4. The method of claim 3, for inhibiting restenosis at a vascular injury site, wherein the rapamycin 40-O-cyclic hydrocarbon ester is administered from a drug-eluting stent placed at the vascular injury site.

5. The method of claim 4, wherein the drug-eluting stent has an expandable stent body formed of one or more filaments, and carried thereon, a coating containing between 20 and 100 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and between 0 and 80 weight percent of a polymer.

6. The method of claim 5, wherein the stent coating contains between 20 and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

7. A drug-eluting stent having an expandable stent body formed of one or more filaments, and carried thereon, a coating containing between 20%-100% rapamycin 40-O-cyclic hydrocarbon ester of claim 1 and between 0 and 80 weight percent of a polymer.

8. The stent of claim 7, wherein the stent coating contains between 20- and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight

percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

9. In an intravascular stent of the type having an expandable stent body formed of one or more filaments, such as a metal-filament stent, and carried thereon, a drug-eluting polymer coating containing 40-80 weight percent polymer and 20 to 60 weight percent of a rapamycin compound having a 40-O-H or 40-O-linear alcohol group, an improvement that significantly reduces the tendency of the coating to flake or crack when the stent body is expanded, comprising substituting for the rapamycin compound, the 40-O-cyclic hydrocarbon ester of claim 1.

10. The stent of claim 9, wherein the drug-eluting polymer coating contains between 20- and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate,poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

11. A pharmaceutical composition comprising microparticles having in particle-entrapped form, 10-80 weight percent the rapamycin 40-O-cyclic hydrocarbon ester of claim 1.

12. The composition of claim 11, wherein the drug-eluting polymer coating contains between 20- and 60 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone),

poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

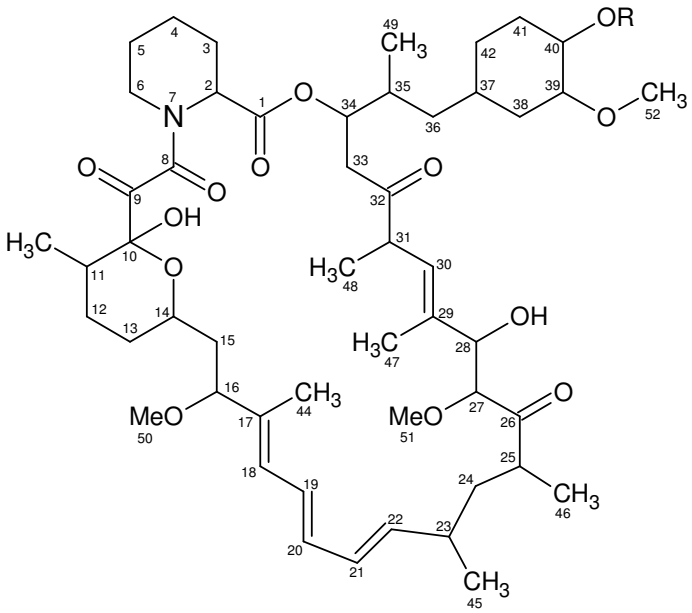
13. A drug-eluting stent having an expandable stent body formed of one or more filaments, and carried thereon, a first coating containing a polymer and a second coating containing between 20%-100% rapamycin 40-O-cyclic hydrocarbon ester of claim 1 and between 0 and 80 weight percent of a polymer.

14. The stent of claim 13, wherein the first stent coating contain at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate,poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.and the second stent coating contains between 20- and 100 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 0 and 80 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

To reduce the rate of restenosis in a PTCA procedure, the stent may be coated with rapamycin or a rapamycin derivative in a form that allows slow release of the drug from the stent against the endothelial cells of the vessel, typically over a two-week to several-month interval. The stent coating may consist of a polymer, e.g., bioerodable polymer, with encapsulated drug, or the drug itself may form a cohesive coating. In either case, the coating may be susceptible to cracking as the stent is expanded at the implantation site, and any loose pieces of coating that break off can be a significant clotting hazard in the bloodstream. Another problem that has been observed heretofore in rapamycin stents is relatively poor drug stability, as evidence by mass balance measurement on the amounts of active drug released from the stent coatings, typically showing less than 40% of active drug recovered after elution from the stent.

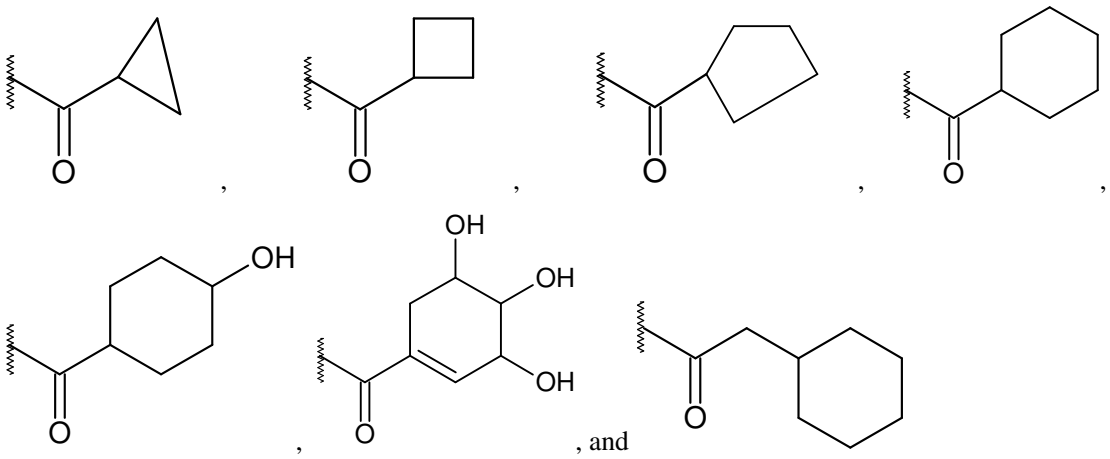
The invention is defined in the independent claims. Some optional features of the invention are defined in the dependent claims.

In one aspect, there is disclosed a rapamycin 40-O-cyclic hydrocarbon ester having the structure:



where R is $C(O)-(CH_2)_n-X$, n is 0, 1 or 2, X is a cyclic hydrocarbon having 3-8 carbons, optionally containing one or more unsaturated bonds, one or more linear-chain or cyclic carbon atoms may contain an OH or halide substitution, and the rapamycin parent structure may contain substitutions at other positions.

Exemplary R groups include:



, , , , , , and

In another aspect, there is disclosed use of a therapeutic amount of the disclosed rapamycin 40-O-cyclic hydrocarbon ester in the manufacture of a medicament for the treatment of any of the following conditions in a mammal: (i) restenosis; (ii) wound healing; (iii) vascular injury; (iv) vascular inflammation; (v) transplantation rejection; (vi) proliferative ophthalmic diseases, including wet age-related macular degeneration (AMD) and diabetic macular edema (DME); (vii) uveitis; (viii) cancer; (ix) various skin conditions such asatopic dermatitis, eczema, tuberous sclerosis, neurofibromatosis, lichen planus and the like; and (x) ear-nose-throat treatments such as sinusitis treatment with sinus stents or balloons. When used to manufacture a medicament for the inhibition of restenosis at a vascular injury site, the rapamycin ester may be provided in a drug-eluting stent which, in use, is placed at the vascular injury site.

Also disclosed is a drug-eluting stent having an expandable stent body formed of one or more filaments and carried on the one or more filaments, a coating containing the above rapamycin 40-O-cyclic hydrocarbon ester. The coating may be formed of the rapamycin compound alone, or formed of a polymer, e.g., bioerodable polymer such as polylactic acid, containing the rapamycin ester in entrapped form. Other suitable polymers include poly(caprolactone), poly(trimethylene carbonate), polyester amide, poly(glycolide), polyhydroxyalkanoates including poly(hydroxyvalerate), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polyorthoester, polyanhydride, poly(glycolic acid). The

stent finds particular use in the inhibition of restenosis at the site of vascular injury and, in use, is placed at the site of vascular injury.

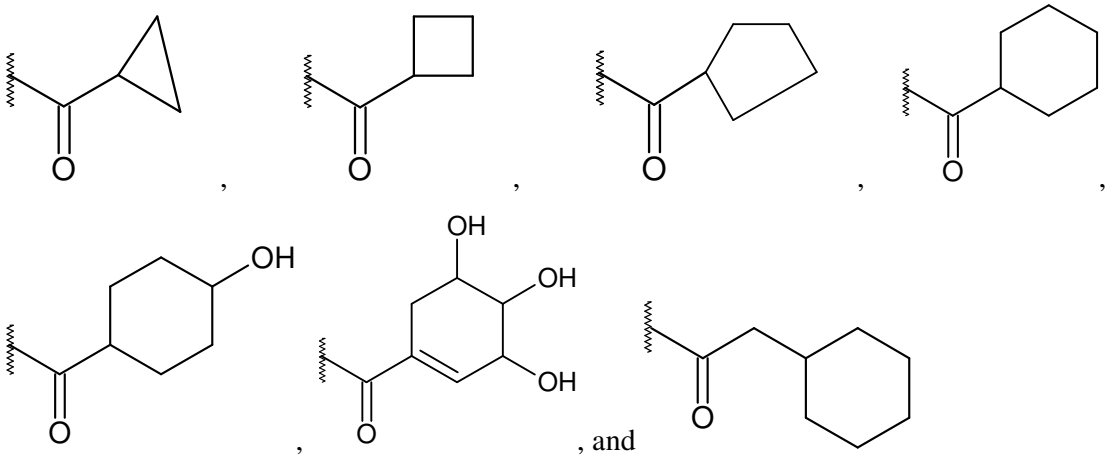
Further disclosed are pharmaceutical compositions, including microparticle compositions, such as liposomes and bioerodable polymer particle compositions, containing the rapamycin ester in an encapsulated or captured form for release over time from a site of administration or implantation of the composition. Microparticles containing the rapamycin analog may be inherently porous with pore sizes ranging from about 5 nanometers to about 10 microns in diameter.

In still another embodiment, there is disclosed an improvement in an intravascular stent of the type having an expandable stent body formed of one or more filaments, such as a metal-filament stent, and carried on the one or more filaments, a polymer coating containing 40%-80% polymer, such as a bioerodable polymer, and 20% to 60% rapamycin compound having a 40-position -OH or $-O(CH)_nOH$ substituent, where n=1 to 5. The improvement, which significantly reduces the tendency of the coating to flake or crack when the stent body is expanded, includes substituting in the rapamycin compound, the disclosed rapamycin 40-O-cyclic hydrocarbon ester.

These and other objects and features of the invention will become more fully apparent when the following detailed description of the invention is read in conjunction with the accompanying figures.

Fig. 1 shows the effects of stent expansion on a polymer coating containing 50 weight percent rapamycin on the stent filaments;

Fig. 2 shows the effects of stent expansion on a polymer coating containing 50 weight percent rapamycin 40-O-cyclic hydrocarbon ester.

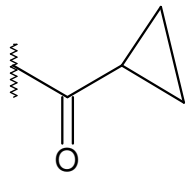
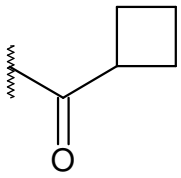
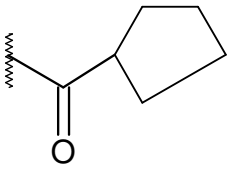
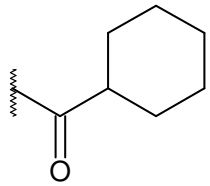
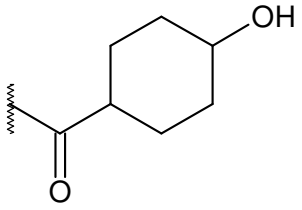
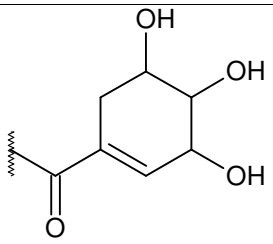
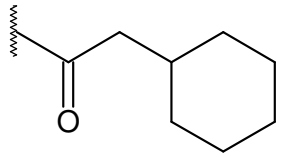


, , , , , , and

II. Synthesis of rapamycin 40-O-cyclic hydrocarbon esters

Table I below shows the R group for a number of exemplary analogs formed in accordance with the present disclosure.

Table I

 **1**	 **2**	 **3**
 **4**	 **5**	 **6**
 **7**		

IIG. Rapamycin 40-O-Cyclic Hydrocarbon Ester with Cyclohexaneacetyl Chloride (Compound 7)

Compound 7 was prepared by dissolving 20 mg rapamycin in 100 µL methylene chloride contained in a 1.5-mL HPLC glass vial with stirring bar and capped. With stirring, 3 µL pyridine was added and followed with 10µL cyclohexaneacetyl chloride, as received. The reaction vessel was placed at ambient temperature and reaction continued with stirring for 1 hour.

The product was analyzed by High Resolution LCMS. Table VIII compares the exact mass calculated and exact mass found for the title compound ($C_{59}H_{91}NO_{14}$) with Na^+ adduct.

Table VIII

$C_{59}H_{91}NO_{14}Na$	
Exact Mass Calculated	1060.6337
Exact Mass Found	1060.6337

III. Compound Properties

IIIA. Increased ductility of a coating formed from the analog

The 40-O-cyclic hydrocarbon rapamycin esters are designed for use in a variety of therapeutic uses, as detailed in Section IV below. One of the important uses is for slow-release of the drug from a stent coating in treating/preventing restenosis following percutaneous transluminal coronary angioplasty (PTCA). In this procedure, the coated stent is delivered to the site of vascular injury in a contracted, low-diameter condition in a balloon catheter, and then expanded to the dimensions of the treated vessel at the site. In this application, it is important that the drug coating is sufficiently ductile that it does not crack or flake off the outer stent surface during stent expansion, since loose pieces of coating, if released into the bloodstream, may present a serious clotting hazard.

In accordance with one of the unexpected advantages, it has been discovered that a coating formed with the compounds disclosed herein is substantially more ductile, i.e., less prone to cracking, than a coating formed with rapamycin. This property can be seen from the photomicrographs of Figs. 1 and 2, which show the condition of a stent coating after stent expansion in a stent formed of a 1:1 weight ratio of a 40-O-cyclic hydrocarbon rapamycin ester and polylactic acid (Fig. 1) and a coating formed of a 1:1 weight ratio of Compound 1 (Table I) and polylactic acid (Fig. 2). As seen, the drug compound disclosed herein provides for a coating that is more ductile, and more resistant to delamination and particle shedding and in general, appears to function as a plasticizer for the polylactate coating. An important advantage of the drug compound in this setting is that a coating with a high drug:polymer ratio can be prepared without the need for addition of a separate plasticizer, which may cause toxic responses, affect drug elution rates, and extend development times and increase production costs.

In one aspect, there includes an improvement in an intravascular stent of the type having an expandable stent body formed of one or more filaments, such as a metal-filament stent, and carried thereon, a drug-eluting polymer coating containing 40-80 weight percent polymer and 20 to 60 weight percent of a rapamycin compound having a 40-O-H or 40-O-linear alcohol group. The improvement, which significantly reduces the tendency of the coating to flake or crack when the stent body is expanded, includes substituting for the rapamycin compound, the disclosed rapamycin 40-O-cyclic hydrocarbon ester.

IIIB. Drug Elution and Stability

This section examines the stability of the disclosed compounds when released from a reservoir over a several-day to several-week period. In one study, a series of stents were prepared with a suitable coating of drug/ polymer mixture. The stents were fabricated from laser cut and electropolished 316L Stainless Steel and measured 16millimeters in length. The coating mixture contained an equal weight of polylactic acid and each of the compounds to be evaluated. The mixture components were weighed, combined in a glass vial with acetone at room temperature and then vortexed until all of the materials

HPLC as above. The amount of drug recovered at each time point and the exhaustive extraction was summed for each stent to determine the total amount of drug recovered, and the results for rapamycin and a rapamycin 40-O-cyclic hydrocarbon ester are shown in the table below.

	Stent #	**Drug Amount (µg)**	**Total Drug (µg) Recovered**	**% Recovery**
Rapamycin	1	238	84.6	35.6
	2	238	103.4	43.4
	3	236	125.2	53.1
	4	236	71.6	32.8
	5	241	109.1	45.3
Average				**42.0**
Standard Deviation				**8.1**
Rapamycin 40-Cyclic Hydrocarbon Ester	6	228	192.5	84.6
	7	233	202.2	87.0
	8	233	198.7	85.3
	9	236	202.4	85.8
	10	241	197.8	82.2
Average				**85.0**
Standard Deviation				**1.8**

Average % recovery for rapamycin and the rapamycin 40-cyclic hydrocarbon ester were 42.0±8.1 and 85.0±1.8, respectively. This indicates that, unexpectedly, drug compounds as disclosed herein are more stable than rapamycin during elution conditions. This property is important as it allows for a lower drug dose to be utilized for patient treatment and also is beneficial for the drug product regulatory approval and quality control purposes because a high in vitro elution recovery is taken as evidence that the drug substance is stable, the test procedure is an accurate monitor of manufacturing quality and good drug product performance can be maintained.

IIIC. Inhibition of Restenosis

Trial A

Stainless steel coronary artery stents coated with the disclosed rapamycin 40-O-cyclic hydrocarbon ester were compared for their ability to control induced restenosis using a 28 day porcine arterial over stretch model. Four different groups of stents were evaluated with the drug compound and in different coating configurations. Group 1 consisted of five stainless steel stents which were first coated with a base layer consisting of a copolymer of polycaprolactone and poly L lactic acid. A topcoat of poly d,l lactic acid and 225 micrograms of rapamycin 40-O- cyclic hydrocarbon ester was then applied. Group 2 consisted of five stainless steel stents with the same base coat and a topcoat of poly d,l lactic acid and 100 micrograms rapamycin 40-O-cyclic hydrocarbon ester. Group 3 consisted of five stents with a drug topcoat consisting only of 100 micrograms of rapamycin 40-O-cyclic hydrocarbon ester applied directly to a base coat of the polycaprolactone-poly L lactic acid copolymer. Finally, Group 4 consisted of five stents with a base coat of parylene polymer and a topcoat of poly d,l lactic acid and 225 micrograms of rapamycin 40-O-cyclic hydrocarbon ester. All of the stents were 16 millimeters in length and were mounted on standard balloon delivery systems and were then sterilized with ethylene oxide gas. The balloon to artery ratio of the deployed stents was approximately 1.20 : 1.00. The matrix of coating layers and drug dosages was chosen with the intent to optimize the adhesion of the active drug compound to the stent surface and to determine the best means to transfer the drug to the surrounding vessel wall upon stent deployment.

The primary objective of this study was to evaluate the drug compound coating on stents to treat vessels in which injury was intentionally induced. Coronary artery measurements were made from angiographic images before stent deployment, immediately after deployment, and twenty-eight days after deployment to determine the effectiveness of the coated stent in reducing restenosis. Determination of angiographic late loss was made by subtraction of the minimum vessel lumen diameter of the stented vessel at 28 days post-

IV. Compositions and Applications

IVA. Compositions

In another aspect, there is disclosed a composition incorporating the disclosed rapamycin 40-O-cyclic hydrocarbon rapamycin ester, where the composition serves a drug reservoir for release, typically in a controlled fashion, of the compound into a treatment site.

Micro and Macro Particles

One exemplary composition includes a suspension of polymer particles that can be introduced into a suitable treatment site *in vivo* via injection or delivery through a catheter. The polymer particles can be microporous, macroporous, or non-porous and can be formed of a polymer that acts as a suitable drug reservoir. Exemplary polymer particles are described, for example, in U.S. Pat. No. 5,135,740, incorporated by reference herein. Liposomal particles that incorporate the compound in encapsulated or membrane-entrapped form are also contemplated. Polymers suitable for particle formation include, but aren't limited to poly(d, l-lactic acid), poly(l-lactic acid), poly(d-lactic acid), poly (glycolic acid) and copolymers and mixtures of polylactate and polyglycolic. Other suitable polymers include methacrylate polymers, such as polybutyl methacrylate, ethylene vinyl alcohol (EVOH), .epsilon.-caprolactone, glycolide, ethylvinyl hydroxylated acetate (EVA), polyvinyl alcohol (PVA), polyethylene oxides (PEO), polyester amides, and co-polymers thereof and mixtures thereof. Typically, the composition is formulated to contain between 20-80 weight percent polymer and 20-80 weight percent rapamycin compound. An exemplary formulation contains between 20 and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight percent of a polylactate or polyglycolate polymer or a polylactate/polyglycolate copolymer or mixed polymer. The particles have typical sizes between about 0.1 micron to about 100 microns in diameter, preferably from about 0.5 microns to about 20 microns, and can be administered as liquid, paste, or gel suspension.

Drug-Coated Stent

In another general embodiment, there is disclosed an endovascular stent coated with the drug alone or the drug formulated in a polymer coated, such as the drug-polymer formulations described above. Such stents are typically cylindrical, expandable metal-frame structures whose struts or filaments may be coated, on their outer surfaces, with a drug-eluting coating. When placed in a body lumen, a stent is expanded to press against the wall of the vessel and hold the stent in place, while drug is eluted from the stent against the wall of the vessel.

An exemplary coating contains equal amounts by weight of compound 1 and d,l PLA material, which may be formulated and applied to the stent outer surface according to well known methods. An example stent product is described in US patent 7,214,759 where polymers containing polyesters and optional therapeutic agents are applied to implantable substrates, including stents. Coatings applied to the surface of stents may incorporate excipient materials along with the rapamycin 40 O-cyclic hydrocarbon esters which enhance the adhesion properties or elution profile of the drug, or impart other beneficial properties to the system. The coating may contain or be composed of micro or macroporous drug reservoirs. The coating may be comprised of the drug compound alone. Those familiar with the art are aware that these examples do not limit the scope of the invention.

IVB. Treating restenosis: compound delivery from a catheter balloon

In another vascular application, rapamycin 40 O-cyclic hydrocarbon esters can be applied as a coating to the surface of the inflatable balloon portion of a percutaneous vascular angioplasty balloon catheter in a manner that when the balloon is placed adjacent to a vascular target lesion and then inflated the drug will separate from the balloon surface and transfer to the affected tissue. In this method of drug delivery the balloon distributes the drug homogenously along the arterial wall, whereas in drug-eluting stents the highest concentration is under the wire components of the stents. Whereas stents generally permanently alter the vessel wall the drug coated balloon is removed after deployment, leaving only the remaining drug and coating. In US patent 7,572,245 Herweck, et al.

describe a means to deliver a therapeutic agent a vessel lumen by positioning a coated balloon within a target vessel and through inflation of the balloon atraumatically smearing the coating agent against the vascular lesion, thus transferring a portion through lipophilic absorptive action. In US patent 7,750,041 Speck, et al. reveal an angiography catheter comprising a coating of paclitaxel and iopromide applied to the balloon portion of the catheter which is released to surrounding tissue upon balloon inflation.

Coatings applied to the surface of vascular balloons may incorporate excipient materials along with the rapamycin 40 O-cyclic hydrocarbon esters which enhance the adhesion properties or elution profile of the drug, or impart other beneficial properties to the system. The coating may contain or be composed of micro or macroporous drug reservoirs. The coating may be comprised of the drug compound alone.

IVC. Treating Ocular Disorders

The compounds disclosed herein may be used to treat ocular disosorders. Rapamycin itself has been evaluated clinically for treatment of macular degeneration. In clinical trials subconjunctival injections of rapamycin in doses ranging from 220 micrograms to 880 micrograms to verify increased visual acuity in a 180 day timeframe. Rapamycin has also been applied systemically in conjunction with corticosteroids for treatment of non-infectious uveitis. The compounds of the subject can be utilized in valved or non-valved stents/shunts used for glaucoma drainage. The ocular disorders may be treated by administering to a mammalian subject in need of treatment, a therapeutic amount of the disclosed rapamycin alkyl ester analog.

IVD. Treating Cancers

The disclosed compounds may also be useful in the treatment of cancer. Rapamycin itself is currently in clinical pancreatic cancer trials as well as skin cancer trials and breast cancer trials. The therapeutic effect of rapamycin and related compounds in cancer and malignant tumor treatment is likely caused by disruption of the biochemical pathways involved in the development of new blood vessels. Rapamycin when combined with cancer

drug Carboplatin have also been found to potentially improve the efficiency of ovarian cancer treatment. Rapamycin has also been shown to inhibit the progression of dermal Kaposi's sarcoma. Other mTOR inhibitors, such as temsirolimus and everolimus are currently being tested for use in cancers such as glioblastoma multiforme and mantle cell lymphoma. As disclosed herein, a cancer may be treated by administereing to a mammalian subject in need of treatment, a therapeutic amount of the disclosed rapamycin 40-O-cyclic hydrocarbon ester analog.

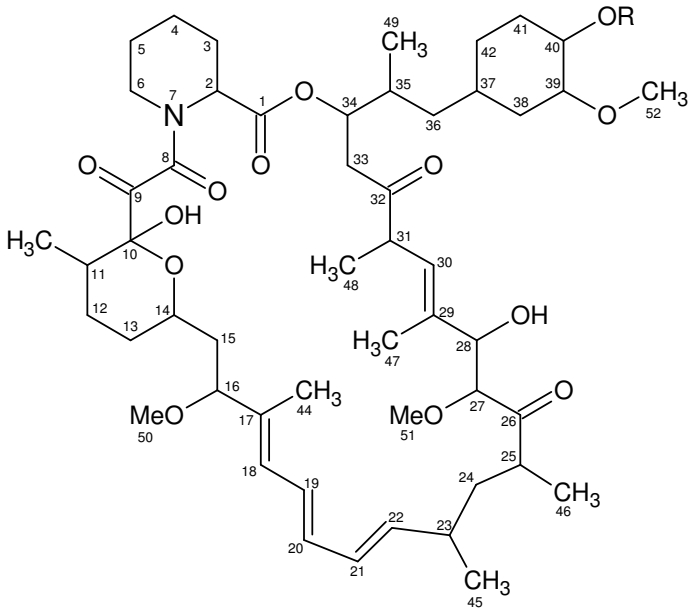
IVE. Prevention of Transplant Rejection

Rapamycin and its analogs can be used alone, or in conjunction with calcineurin inhibitors, such as tacrolimus to provide immunosuppression regimens. Transplant patients can be given oral medications which include rapamycin under the trade name Rapamune® or everolimus, a rapamycin analog under the trade name Certican® to reduce the incidence of tissue rejection. These therapies have the advantage of having lower toxicity toward kidneys. The subject may be treated by administering a therapeutic amount of the disclosed rapamycin alkyl ester analog.

Although the invention has been described with respect to particular embodiments and applictions, it will be appreciated that various additional modification the applications may be made consistent with the scope of the claims.

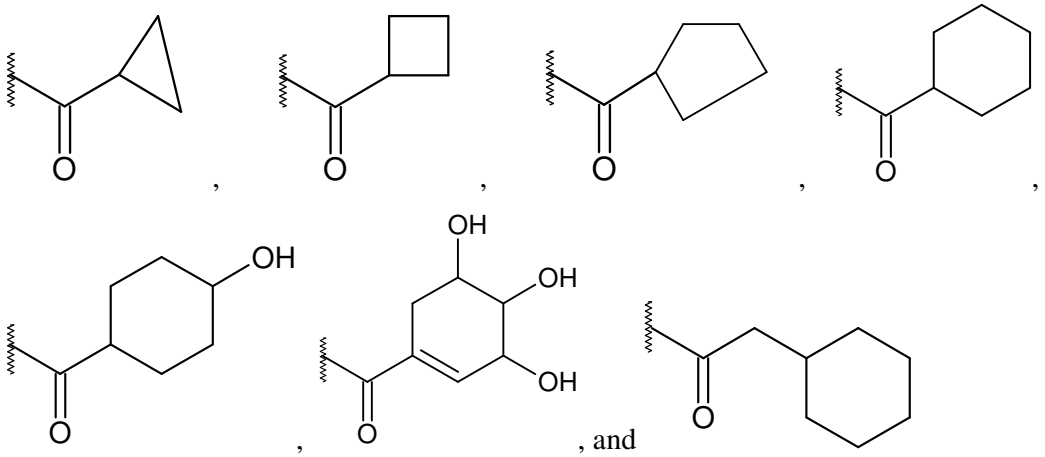
PATENT CLAIMS

1. A rapamycin 40-O-cyclic hydrocarbon ester compound having the structure:



where R is $C(O)-(CH_2)_n-X$, n is 0, 1 or 2, and X is a cyclic hydrocarbon having 3-8 carbons; wherein X optionally contains one or more unsaturated bonds, one or more linear-chain or cyclic carbon atoms and/or an OH or halide substitution; and wherein the rapamycin parent structure optionally contains substitutions at non-40 positions.

2. The compound of claim 1, wherein $C(O)-(CH_2)_n-X$ has one of the structures:



3. Use of a therapeutic amount of the rapamycin 40-O-cyclic hydrocarbon ester of claim 1 or claim 2 in the manufacture of a medicament for the treatment of a medical condition selected from: (i) restenosis; (ii) wound healing; (iii) vascular injury; (iv) vascular inflammation; (v) transplantation rejection; (vi) proliferative ophthalmic diseases, including wet age-related macular degeneration (AMD) and diabetic macular edema (DME); (vii) uveitis, and (viii) cancer in a mammal. .

4. The use of claim 3, wherein the medicament is for the inhibition of restenosis at a vascular injury site, and wherein the rapamycin 40-O-cyclic hydrocarbon ester is provided in a drug-eluting stent.

5. The use of claim 4, wherein the drug-eluting stent has an expandable stent body formed of one or more filaments, and carried thereon, a coating containing between 20 and 100 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and between 0 and 80 weight percent of a polymer.

6. The use of claim 5, wherein the stent coating contains between 20 and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

7. A drug-eluting stent having an expandable stent body formed of one or more filaments, and carried thereon, a coating containing between 20%-100% of the rapamycin 40-O-cyclic hydrocarbon ester of claim 1 or claim 2 and between 0 and 80 weight percent of a polymer.

8. The stent of claim 7, wherein the stent coating contains between 20- and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight

percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

9. In an intravascular stent of the type having an expandable stent body formed of one or more filaments, such as a metal-filament stent, and carried thereon, a drug-eluting polymer coating containing 40-80 weight percent polymer and 20 to 60 weight percent of a rapamycin compound having a 40-O-H or 40-O-linear alcohol group, an improvement that significantly reduces the tendency of the coating to flake or crack when the stent body is expanded, comprising substituting for the rapamycin compound, the 40-O-cyclic hydrocarbon ester of claim 1.

10. The stent of claim 9, wherein the drug-eluting polymer coating contains between 20- and 60 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 40 and 80 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate,poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

11. A pharmaceutical composition comprising microparticles having in particle-entrapped form, 10-80 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester of claim 1 or claim 2.

12. The composition of claim 11, wherein the microparticles comprise a drug-eluting polymer coating containing between 20- and 60 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone),

poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

13. A drug-eluting stent having an expandable stent body formed of one or more filaments, and carried thereon, a first coating containing a polymer and a second coating containing between 20%-100% of the rapamycin 40-O-cyclic hydrocarbon ester of claim 1 or claim 2 and between 0 and 80 weight percent of a polymer.

14. The stent of claim 13, wherein the first stent coating contain at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, polyhydroxyalkanoate,poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.and the second stent coating contains between 20- and 100 weight percent of the rapamycin 40-O-cyclic hydrocarbon ester and 0 and 80 weight percent of at least one polymer selected from the group consisting of polyanhydride, poly(glycolic acid), poly(glycolide), poly(L-lactide), poly(d,l-lactide), poly(L-lactic acid), poly(d,l-lactic acid), poly(caprolactone), poly(trimethylene carbonate), polyester amide, poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), and polyorthoester.

15. The rapamycin 40-O-cyclic hydrocarbon ester of claim 1 or claim 2 for use as a medicament.