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- (54) **WATER SOLUBLE RAPAMYCIN ESTERS**
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- (*) **Notice:** **Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.**
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- (51) **Int. Cl.⁷** **C07D 498/16; C07D 498/18; C07D 491/06; A61K 31/395; A61K 31/445**
- (52) **U.S. Cl.** **514/291; 540/456**
- (58) **Field of Search** **540/456; 514/291**
- (56) **References Cited**

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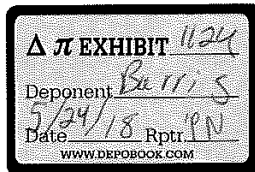
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(57) **ABSTRACT**

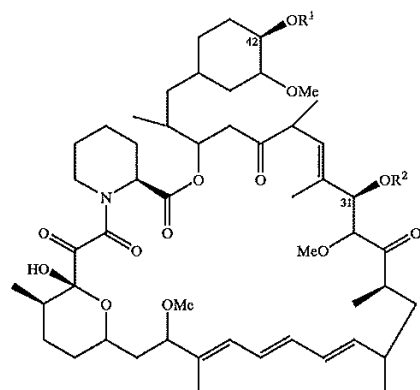
This invention provide pegylated hydroxyesters of rapamycin which are useful in inducing immunosuppression and in the treatment of transplantation rejection, autoimmune diseases, solid tumors, fungal infections, and vascular disease.

18 Claims, No Drawings



Breckenridge Exhibit 1092
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wherein

R^1 and R^2 are each, independently, hydrogen or $-\text{CO}(\text{CR}^3\text{R}^4)_b(\text{CR}^5\text{R}^6)_d\text{CR}^7\text{R}^8\text{R}^9$;

R^3 and R^4 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, trifluoromethyl, or $-\text{F}$;

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

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R^7 is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_g\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$;

R^8 and R^9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, $-(\text{CR}^3\text{R}^4)_j\text{OR}^{10}$, $-\text{CF}_3$, $-\text{F}$, or $-\text{CO}_2\text{R}^{11}$;

R^{10} is hydrogen or $-\text{COCH}_2-\text{S}-\text{CH}_2\text{CH}_2-(\text{O}-\text{CH}_2-\text{CH}_2)_n-\text{OCH}_3$;

R^{11} is hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, or phenylalkyl of 7-10 carbon atoms;

$b=0-6$;

$d=0-6$;

$f=0-6$;

$n=5-450$;

with the proviso that R^1 and R^2 are both not hydrogen and further provided that either R^1 or R^2 contains at least one $-(\text{CR}^3\text{R}^4)_g\text{OR}^{10}$ group in which R^{10} is $-\text{COCH}_2-\text{S}-\text{CH}_2\text{CH}_2-(\text{O}-\text{CH}_2-\text{CH}_2)_n-\text{OCH}_3$, or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier.

17. A compound which is rapamycin 42-ester with 3-hydroxy-2-(2-iodo-acetoxymethyl)-2-methyl-propionic acid.

18. A compound which is rapamycin 42-ester with 3-(2-iodo-acetoxy)-2-(2-iodo-acetoxymethyl)-2-methyl-propionic acid.

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