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(63) Continuation of application No. 10/393,795, filed on Mar. 21, 2003, now Pat. No. 6,852,729, which is a continuation of application No. 09/866,977, filed on May 29, 2001, now Pat. No. 6,605,613, which is a continuation of application No. PCT/EP99/09521, filed on Dec. 6, 1999.

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(57) **ABSTRACT**  
A mixture comprising a poly-ene macrolide and an antioxidant. Preferably, the poly-ene macrolide is rapamycin and the antioxidant is 2, 6-di-tert-butyl-4-methylphenol. The presence of the antioxidant improves the stability of the poly-ene macrolide to oxidation.

(51) **Int. Cl.**  
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**12 Claims, 4 Drawing Sheets**

FIGURE 1/3

Atomic coordinates and equivalent isotropic displacement parameters ( $\text{\AA}^2$ )  
 ( $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor)

	x/a	y/b	z/c	U(eq)
C(1)	.9065(6)	.0121(9)	.5077(5)	.060(2)
O(1)	.9239(4)	-.0736(6)	.5482(4)	.076(2)
C(2)	.8041(5)	.0615(8)	.4625(4)	.060(2)
C(3)	.7847(7)	.1748(10)	.4984(6)	.087(3)
C(4)	.7627(7)	.1515(10)	.5725(7)	.098(3)
C(5)	.6795(7)	.0653(11)	.5610(6)	.094(3)
C(6)	.7005(6)	-.0496(9)	.5256(5)	.074(3)
N(7)	.7272(4)	-.0269(6)	.4567(4)	.059(2)
C(8)	.6781(5)	-.0693(7)	.3883(5)	.055(2)
O(8)	.6965(4)	-.0432(6)	.3287(3)	.074(2)
C(9)	.5940(6)	-.1566(8)	.3784(5)	.056(2)
O(9)	.6074(4)	-.2513(6)	.4074(4)	.084(2)
C(10)	.4962(5)	-.1136(8)	.3223(5)	.057(2)
O(10)	.5045(4)	-.1009(6)	.2486(3)	.075(2)
C(11)	.4079(6)	-.1951(8)	.3160(5)	.068(3)
C(11M)	.4107(7)	-.3114(9)	.2776(6)	.088(3)
C(12)	.3135(6)	-.1252(10)	.2738(6)	.088(3)
C(13)	.3099(6)	-.0061(10)	.3115(7)	.099(4)
C(14)	.4002(6)	.0651(9)	.3156(6)	.078(3)
O(14)	.4868(4)	-.0019(5)	.3559(3)	.065(2)
C(15)	.4070(6)	.01811(10)	.3592(6)	.082(3)
C(16)	.4953(7)	.2564(8)	.3624(6)	.079(3)
O(16)	.4841(5)	.3639(6)	.4015(4)	.095(2)
C(16M)	.5697(8)	.4308(10)	.4288(7)	.102(3)
C(17)	.5056(6)	.2802(9)	.2841(6)	.073(3)
C(17M)	.4268(7)	.3541(11)	.2307(6)	.103(4)
C(18)	.5806(7)	.2368(10)	.2680(6)	.079(3)
C(19)	.6018(7)	.2458(11)	.1964(6)	.092(3)
C(20)	.6768(8)	.1937(12)	.1809(6)	.097(3)
C(21)	.7032(8)	.2069(13)	.1094(7)	.111(4)
C(22)	.7771(8)	.1565(15)	.0948(7)	.121(5)
C(23)	.8086(8)	.1781(16)	.0240(6)	.128(5)
C(23M)	.7254(9)	.2152(23)	.0474(7)	.184(9)
C(24)	.8912(8)	.2643(18)	.0406(6)	.140(6)
C(25)	.9826(9)	.2329(20)	.1069(6)	.141(6)
C(25M)	1.0348(12)	.1245(20)	.0884(8)	.178(8)
C(26)	1.0512(10)	.3412(22)	.1293(7)	.157(8)
O(26)	1.1132(8)	.3601(21)	.0998(7)	.281(11)
C(27)	1.0375(8)	.4278(16)	.1891(7)	.118(5)
O(27)	1.0877(7)	.5366(13)	.1901(7)	.185(5)
C(27M)	1.0445(17)	.6202(22)	.1382(13)	.256(13)
C(28)	1.0824(7)	.3750(11)	.2699(6)	.091(3)
O(28)	1.1827(4)	.3501(7)	.2818(4)	.108(2)

FIGURE 1/3 (Cont.)

Atomic coordinates and equivalent isotropic displacement parameters ( $\text{\AA}^2$ )  
(cont.)

	x/a	y/b	z/c	U(eq)
C(29)	1.0329(7)	.2733(10)	.2922(5)	.073(3)
C(29M)	.9318(6)	.2995(10)	.2984(6)	.094(3)
C(30)	1.0764(7)	.1700(10)	.3100(5)	.077(3)
C(31)	1.0376(7)	.0581(10)	.3340(5)	.081(3)
C(31M)	1.0198(9)	-.0385(13)	.2723(7)	.124(4)
C(32)	1.1046(7)	.0210(10)	.4103(6)	.079(3)
O(32)	1.1436(7)	-.0747(9)	.4183(5)	.132(3)
C(33)	1.1271(6)	.1025(9)	.4776(5)	.071(3)
C(34)	1.0764(5)	.0601(8)	.5342(5)	.062(2)
O(34)	.9735(3)	.0853(5)	.4967(3)	.071(2)
C(35)	1.1115(5)	.1217(9)	.6132(5)	.064(2)
C(35M)	1.1060(7)	.2562(10)	.6069(6)	.092(3)
C(36)	1.2149(6)	.0757(9)	.6578(5)	.072(3)
C(37)	1.2650(6)	.1298(9)	.7370(5)	.074(3)
C(38)	1.2091(7)	.1198(14)	.7935(5)	.110(4)
C(39)	1.2680(9)	.1650(16)	.8735(6)	.128(5)
O(39)	1.2082(8)	.1584(20)	.9206(6)	.243(9)
C(39M)	1.2099(20)	.2512(47)	.9702(17)	.498(36)
C(40)	1.3640(9)	.0982(13)	.9048(6)	.0116(4)
O(40)	1.4177(7)	.1412(10)	.9790(5)	.151(4)
C(41)	1.4221(7)	.1138(13)	.8506(6)	.110(4)
C(42)	1.3653(6)	.0697(11)	.7702(5)	.096(3)
C(43)	1.4272(14)	.0621(20)	1.0408(9)	.171(7)
C(44)	1.5146(20)	-.0307(24)	1.0549(10)	.238(12)
O(45)	1.4956(12)	-.1215(13)	.9899(7)	.215(5)

FIGURE 2/3

## Bond lengths (Å)

C(1)-O(1)	1.193(10)	C(24)-C(25)	1.52(2)
C(1)-O(34)	1.329(10)	C(25)-C(25M)	1.53(2)
C(1)-C(2)	1.545(11)	C(25)-C(26)	1.54(3)
C(2)-N(7)	1.465(10)	C(26)-O(26)	1.20(2)
C(2)-C(3)	1.500(13)	C(26)-C(27)	1.53(2)
C(3)-C(4)	1.511(14)	C(27)-O(27)	1.42(2)
C(4)-C(5)	1.502(13)	C(27)-C(28)	1.533(14)
C(5)-C(6)	1.518(14)	O(27)-C(27M)	1.34(2)
C(6)-N(7)	1.453(10)	C(28)-O(28)	1.415(10)
N(7)-C(8)	1.315(9)	C(28)-C(29)	1.471(14)
C(8)-O(8)	1.237(9)	C(29)-C(30)	1.311(13)
C(8)-C(9)	1.523(11)	C(29)-C(29M)	1.523(12)
C(9)-O(9)	1.178(9)	C(30)-C(31)	1.497(14)
C(9)-C(10)	1.532(11)	C(31)-C(32)	1.482(13)
C(10)-O(10)	1.398(9)	C(31)-C(31M)	1.53(2)
C(10)-O(14)	1.425(10)	C(32)-O(32)	1.201(11)
C(10)-C(11)	1.540(11)	C(32)-C(33)	1.487(13)
C(11)-C(11M)	1.491(13)	C(33)-C(34)	1.521(11)
C(11)-C(12)	1.546(12)	C(34)-O(34)	1.447(9)
C(12)-C(13)	1.51(2)	C(34)-C(35)	1.537(11)
C(13)-C(14)	1.506(13)	C(35)-C(35M)	1.517(13)
C(14)-O(14)	1.441(10)	C(35)-C(36)	1.540(11)
C(14)-C(15)	1.516(14)	C(36)-C(37)	1.525(12)
C(15)-C(16)	1.511(12)	C(37)-C(38)	1.503(11)
C(16)-O(16)	1.439(11)	C(37)-C(42)	1.532(12)
C(16)-C(17)	1.512(14)	C(38)-C(39)	1.526(14)
O(16)-C(16M)	1.392(11)	C(39)-O(39)	1.399(13)
C(17)-C(18)	1.301(12)	C(39)-C(40)	1.51(2)
C(17)-C(17M)	1.491(13)	O(39)-C(39M)	1.38(4)
C(18)-C(19)	1.441(14)	C(40)-O(40)	1.417(13)
C(19)-C(20)	1.333(14)	C(40)-C(41)	1.50(2)
C(20)-C(21)	1.48(2)	O(40)-C(43)	1.41(2)
C(21)-C(22)	1.30(2)	C(41)-C(42)	1.521(14)
C(22)-C(23)	1.52(2)	C(43)-C(44)	1.59(3)
C(23)-C(24)	1.49(2)	C(44)-O(45)	1.52(2)
C(23)-C(23M)	1.52(2)		

FIGURE 3/3

## Bond angles (°)

O(1)-C(1)-O(34)	125.1(7)	C(23)-C(24)-C(25)	116(2)
O(1)-C(1)-C(2)	126.8(8)	C(24)-C(25)-C(25M)	111.7(14)
O(34)-C(1)-C(2)	108.0(8)	C(24)-C(25)-C(26)	110(2)
N(7)-C(2)-C(3)	111.5(6)	C(25M)-C(25)-C(26)	111.9(12)
N(7)-C(2)-C(1)	111.3(7)	O(26)-C(26)-C(27)	120(2)
C(3)-C(2)-C(1)	110.4(7)	O(26)-C(26)-C(25)	122(2)
C(2)-C(3)-C(4)	111.6(9)	C(27)-C(26)-C(25)	118.5(12)
C(5)-C(4)-C(3)	111.8(9)	O(27)-C(27)-C(26)	112.2(12)
C(4)-C(5)-C(6)	110.6(7)	O(27)-C(27)-C(28)	105.4(12)
N(7)-C(6)-C(5)	111.4(8)	C(26)-C(27)-C(28)	109.5(12)
C(8)-N(7)-C(6)	123.5(7)	C(27M)-O(27)-C(27)	118.5(14)
C(8)-N(7)-C(2)	118.6(7)	O(28)-C(28)-C(29)	111.3(9)
C(6)-N(7)-C(2)	117.3(6)	O(28)-C(28)-C(27)	108.7(8)
O(8)-C(8)-N(7)	123.6(7)	C(29)-C(28)-C(27)	118.4(10)
O(8)-C(8)-C(9)	115.6(7)	C(30)-C(29)-C(28)	121.5(9)
N(7)-C(8)-C(9)	120.8(8)	C(30)-C(29)-C(29M)	122.9(10)
O(9)-C(9)-C(8)	121.3(7)	C(28)-C(29)-C(29M)	115.4(9)
O(9)-C(9)-C(10)	124.8(8)	C(29)-C(30)-C(31)	128.7(9)
C(8)-C(9)-C(10)	113.6(7)	C(32)-C(31)-C(30)	108.8(8)
O(10)-C(10)-O(14)	112.1(7)	C(32)-C(31)-C(31M)	113.7(10)
O(10)-C(10)-C(9)	109.7(6)	C(30)-C(31)-C(31M)	111.8(8)
O(14)-C(10)-C(9)	100.5(6)	O(32)-C(32)-C(31)	120.3(11)
O(10)-C(10)-C(11)	108.1(6)	O(32)-C(32)-C(33)	118.8(10)
O(14)-C(10)-C(11)	111.6(6)	C(31)-C(32)-C(33)	120.8(9)
C(9)-C(10)-C(11)	114.9(7)	C(32)-C(33)-C(34)	110.2(8)
C(11M)-C(11)-C(10)	114.3(7)	O(34)-C(34)-C(33)	104.8(6)
C(11M)-C(11)-C(12)	111.2(8)	O(34)-C(34)-C(35)	109.8(6)
C(10)-C(11)-C(12)	107.9(7)	C(33)-C(34)-C(35)	114.5(7)
C(13)-C(12)-C(11)	111.9(8)	C(1)-O(34)-C(34)	119.2(7)
C(14)-C(13)-C(12)	109.9(9)	C(35M)-C(35)-C(34)	112.6(8)
O(14)-C(14)-C(13)	109.8(8)	C(35M)-C(35)-C(36)	113.2(8)
O(14)-C(14)-C(15)	106.2(7)	C(34)-C(35)-C(36)	108.6(7)
C(13)-C(14)-C(15)	113.2(8)	C(37)-C(36)-C(35)	116.9(8)
C(10)-O(14)-C(14)	115.1(6)	C(38)-C(37)-C(36)	115.6(7)
C(16)-C(15)-C(14)	114.5(7)	C(38)-C(37)-C(42)	109.6(8)
O(16)-C(16)-C(15)	105.4(7)	C(36)-C(37)-C(42)	107.5(8)
O(16)-C(16)-C(17)	112.5(8)	C(37)-C(38)-C(39)	112.5(8)
C(15)-C(16)-C(17)	113.4(8)	O(39)-C(39)-C(40)	113.9(13)
C(16M)-O(16)-C(16)	114.0(7)	O(39)-C(39)-C(38)	108.2(10)
C(18)-C(17)-C(17M)	124.9(9)	C(40)-C(39)-C(38)	111.0(11)
C(18)-C(17)-C(16)	119.2(9)	C(39)-O(39)-C(39M)	119(2)
C(17M)-C(17)-C(16)	115.9(8)	O(40)-C(40)-C(41)	110.3(10)
C(17)-C(18)-C(19)	127.7(10)	O(40)-C(40)-C(39)	110.2(12)
C(20)-C(19)-C(18)	125.6(11)	C(41)-C(40)-C(39)	108.9(10)
C(19)-C(20)-C(21)	126.6(11)	C(43)-O(40)-C(40)	115.9(12)
C(22)-C(21)-C(20)	126.3(12)	C(40)-C(41)-C(42)	111.2(9)
C(21)-C(22)-C(23)	126.0(13)	C(41)-C(42)-C(37)	112.8(9)
C(24)-C(23)-C(23M)	111(2)	O(40)-C(43)-C(44)	114(2)
C(24)-C(23)-C(22)	111.4(10)	O(45)-C(44)-C(43)	112.2(14)
C(23M)-C(23)-C(22)	114.2(10)		

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