MBA (rel. IC50)	2.2
IL-6 dep. prol. (rel. IC50)	2.8
MLR (rel. IC50)	3.4

Example 9: 40-O-(3-Hydroxy)propyl-rapamycin

a) 40-O-[3-(t-Butyldimethylsilyl)oxy]propyl-rapamycin

The same procedure as described in example 8, step a) using 3-(t-butyldimethylsilyl)oxyprop-1-yl triflate affords 40-O-[3-(t-butyldimethylsilyl)oxy]propyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.05 (6H, s), 0.72 (1H, dd), 0.90 (9H, s), 1.65 (3H, s), 1.74 (3H, s), 1.77 (2H, m), 3.03 (1H, m), 3.52–3.73 (7H, m); MS (FAB) m/z 1108 ([M+Na]$^+$), 1036 ([M-(OCH_3+H_2O)]$^+$).

b) 40-O-(3-Hydroxy)propyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 1.80 (2H, m), 3.05 (1H, m), 3.55–3.91 (8H, m); MS (FAB) m/z 994 ([M+Na]$^+$), 940 ([M-(OCH_3)]$^+$), 922 ([M-(OCH_3+H_2O)]$^+$), 904 ([M-(OCH_3+2H_2O)]$^+$), 872 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.6
IL-6 dep. prol. (rel. IC50)	2.7
MLR (rel. IC50)	11

Example 10: 40-O-(6-Hydroxy)hexyl-rapamycin

a) 40-O-[6-(t-Butyldimethylsilyl)oxy]hexyl-rapamycin

The same procedure as described in example 8, step a) using 6-(t-butyldimethylsilyl)oxyhex-1-yl triflate affords 40-O-[6-(t-Butyldimethylsilyl)oxy]hexyl-rapamycin: MS (FAB) m/z 1150 ([M+Na]$^+$).

b) 40-O-(6-Hydroxy)hexyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.38 (2H, m), 1.57 (4H, m), 1.65 (3H, s), 1.74 (3H, s), 3.02 (1H, m), 3.49–3.72 (8H, m); MS (FAB) m/z 1036 ([M+Na]$^+$), 982 ([M-(OCH_3)]$^+$), 964 ([M-(OCH_3+H_2O)]$^+$), 946 ([M-(OCH_3+2H_2O)]$^+$), 914 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	0.8
IL-6 dep. prol. (rel. IC50)	8.5
MLR (rel. IC50)	18

Example 11: 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin

a) 40-O-[2-t-Butyldimethylsilyl)oxyethoxy]ethyl-rapamycin

The same procedure as described in example 8, step a) using 2-[2-(t-butyldimethylsilyl)oxy-ethoxy]ethyl triflate affords 40-O-[2-(t-butyldimethylsilyl)oxyethoxy]ethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.71 (1H, dd), 0.88 (9H, s), 1.65 (3H, s), 1.74 (3H, s), 3.07 (1H, m), 3.51–3.79 (11H, m); MS (FAB) m/z 1138 ([M+Na]$^+$), 1115 (M$^+$), 1097 ([M-H_2O]$^+$), 1084 ([M-(OCH_3)]$^+$), 1066 ([M-(OCH_3+H_2O)]$^+$), 1048 ([M-(OCH_3+2H_2O)]$^+$), 1034 ([M-(2CH_3OH+OH)]$^+$), 1016 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

b) 40-O-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin

Treatment of the compound obtained in step a) in the conditions described in example 8, step b) yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.74 (3H, s), 3.05 (1H, m), 3.51–3.77 (11H, m); MS (FAB) m/z 1024 ([M+Na]$^+$), 1001 (M$^+$), 983 ([M-H_2O]$^+$), 970 ([M-(OCH_3)]$^+$), 952 ([M-(OCH_3+H_2O)]$^+$), 934 ([M-(OCH_3+2H_2O)]$^+$), 920 ([M-(2CH_3OH+OH)]$^+$), 902 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.2
IL-6 dep. prol. (rel. IC50)	3.2
MLR (rel. IC50)	2

Example 12: 40-O-[(3S)-2,2-Dimethyldioxolan-3-yl] methyl-rapamycin

The same procedure as described in example 8, step a) using the triflate of glycerol acetonide affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.36 (3H, s), 1.42 (3H, s), 1.65 (3H, s), 1.75 (3H, s), 3.06 (1H, m), 3.55 (2H, m), 3.69 (3H, m), 4.06 (1H, dd), 4.26 (1H, m); MS (FAB) m/z 1050 ([M+Na]$^+$), 996 ([M-(OCH_3)]$^+$), 978 ([M-(OCH_3+H_2O)]$^+$), 960 ([M-(OCH_3+2H_2O)]$^+$).

MBA (rel. IC50)	0.9
IL-6 dep. prol. (rel. IC50)	8
MLR (rel. IC50)	290

Example 13: 40-O-[(2S)-2,3-Dihydroxyprop-1-yl]-rapamycin

Treatment of the compound obtained in the previous example in the conditions described in example 3 yields the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.07 (1H, m), 3.68 (8H, m); MS (FAB) m/z 1010 ([M+Na]$^+$), 956 ([M-(OCH_3)]$^+$), 938 ([M-(OCH_3+H_2O)]$^+$), 920 ([M-(OCH_3+2H_2O)]$^+$), 888 ([M-(OCH_3+CH_3OH 2H_2O)]$^+$).

MBA (rel. IC50)	0.67
IL-6 dep. prol. (rel. IC50)	9
MLR (rel. IC50)	10

Example 14: 40-O-(2-Acetoxy)ethyl-rapamycin

To a stirred, cooled (0° C.) solution of 53 mg (0.055 mmol) of 40-O-hydroxyethyl-rapamycin in 2 mL of methylene chloride is added 0.2 mL of pyridine followed by 0.02 mL (0.281 mmol) of acetyl chloride. The mixture is stirred for 3 h and diluted with ethyl acetate, then washed with aq. sodium bicarbonate, cold 1N HCl and again with aq. sodium bicarbonate. The organic solution is dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (30:70 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 2.08 (3H, s), 3.07 (1H, m), 3.78 (2H, dd), 4.20 (2H, dd); MS (FAB) m/z 1022 ([M+Na]$^+$), 999 (M$^+$), 982 ([M-(OH]$^+$), 968 ([M-(OCH_3]$^+$), 950 ([M-(OCH_3+H_2+H_2O)]$^+$), 932 ([M-(OCH_3+2H_2O)]$^+$), 918 ([M-(2CH_3OH+OH)]$^+$), 900 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	2
IL-6 dep. prol. (rel. IC50)	7.6
MLR (rel. IC50)	3.6

Example 15: 40-O-(2-Nicotinoyloxy)ethyl-rapamycin

The same procedure as described in the previous example using nicotinoyl chloride hydrochloride affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.65 (3H, s), 1.75 (3H, s), 3.07 (1H, m), 3.94 (2H, dd), 4.49 (2H, t), 7.39 (1H, dd), 8.31 (1H, ddd), 8.78 (1H, ddd), 9.24 (1H, dd); MS (FAB) m/z 1085 ([M+Na]$^+$), 1063 ([M+H]$^+$), 1045

([M-OH]$^+$), 1031 ([M-(OCH_3)]$^+$), 1013 ([M-(OCH_3+H_2O)]$^+$).

MBA (rel. IC50)	1.1
IL-6 dep. prol. (rel. IC50)	6.9
MLR (rel. IC50)	5

Example 16: 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin

a) 40-O-(2-Bromoacetoxy)ethyl-rapamycin

The same procedure as described in example 14 using bromoacetyl chloride affords 40-O-(2-bromoacetoxy)ethyl-rapamycin: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.76 (3H, s), 3.03 (1H, m), 3.82 (2H, m), 3.87 (2H, s), 4.31 (2H, m); MS (FAB) m/z 1100, 1102 ([M+Na]$^+$), 1077 (M$^+$), 1061 ([M-H_2O]$^+$), 1046, 1048 ([M-(OCH_3)]$^+$), 1028, 1030 ([M-(OCH_3+H_2O)]$^+$), 1012 ([M-(OCH_3+2H_2O)]$^+$), 996 ([M-(2CH_3OH+OH)]$^+$), 980 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

b) 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin

To a stirred, cooled (−45° C.) solution of 54 mg (0.05 mmol) of 40-O-(2-bromoacetoxy)ethyl-rapamycin in 0.5 mL of DMF is added a solution of 0.022 mL (0.25 mmol) of morpholine in 0.2 mL of DMF and the resulting mixture is stirred at that temperature for 1 h, then treated with aq. sodium bicarbonate. This mixture is extracted three times with ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (95:5 ethyl acetate-methanol) yielding the title compound as an amorphous white solid: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.76 (3H, s), 2.60 (3H, m), 3.07 (1H, m), 3.24 (2H, s), 3.78 (8H, m), 4.27 (2H, t); MS (FAB) m/z 1107 ([M+Na]$^+$), 1085 ([M+H]$^+$), 1067 ([M-OH]$^+$), 1053 ([M-(OCH_3)]$^+$), 1035 ([M-(OCH_3+H_2O)]$^+$).

MBA (rel. IC50)	1.3
IL-6 dep. prol. (rel. IC50)	4
MLR (rel. IC50)	3.5

Example 17: 40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin

The same procedure as described in example 16, step b) using imidazole affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.78 (3H, s), 3.06 (3H, m), 3.80 (2H, m), 4.32 (2H, m), 4.73 (2H, s), 6.97 (1H, dd), 7.09 (1H, dd), 7.52 (1H, dd); MS (FAB) m/z 1066 ([M+Na]$^+$), 1048 ([M+OH]$^+$), 1034 ([M-(OCH_3)]$^+$), 1016 ([M-(OCH_3+H_2O)]$^+$).

MBA (rel. IC50)	1
IL-6 dep. prol. (rel. IC50)	7.6
MLR (rel. IC50)	3.4

Example 18: 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy] ethyl-rapamycin

The same procedure as described in example 16, step b) using N-methylpiperazine affords the title compound: ^{1}H NMR ($CDCl_3$) δ0.72 (1H, dd), 1.67 (3H, s), 1.77 (3H, s), 2.78 (4H, s and m), 3.02 (4H, bs), 3.08 (1H, m), 3.32 (2H, s), 3.80 (2H, dd), 4.27 (2H, t); MS (FAB) m/z 1098 ([M+Na]$^+$), 1066 ([M-(OCH_3)]$^+$).

MBA (rel. IC50)	2.6
IL-6 dep. prol. (rel. IC50)	10.3
MLR (rel. IC50)	5

Example 19: 39-O-Desmethyl-39,40-O,O-ethylene-rapamycin

To a stirred, cooled (−20° C.) solution of 48 mg (0.05 mmol) of 40-O-hydroxyethyl-rapamycin and 0.023 mL (0.20 mmol) of 2,6-lutidine in 0.5 mL of methylene chloride is added 0.008 mL (0.05 mmol) of triflic anhydride. The mixture is stirred at this temperature for 2 h, then allowed to warm to room temperature and stirred for one more hour. The reaction is quenched with aq. sodium bicarbonate and the resulting mixture is extracted with three portions of ethyl acetate. The organic solution is washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (30:70 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ1.66 (3H, s), 1.75 (3H, s), 3.14 (3H, s), 3.35 (3H, s), 3.76 (4H, s); MS (FAB) m/z 948 ([M+Na]$^+$), 925 (M$^+$), 908 ([M-OH]$^+$), 894 ([M-(OCH_3)]$^+$), 876 ([M-(OCH_3+H_2O)]$^+$), 858 ([M-(OCH_3+2H_2O)]$^+$), 844 ([M-(2CH_3OH+OH)]$^+$), 826 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	1.6
IL-6 dep. prol. (rel. IC50)	22.9
MLR (rel. IC50)	16

Example 20: (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin

a) (26R)-26-Dihydro-40-O-[2-(t-Butyldimethylsilyloxy)] ethyl-rapamycin

In 4.5 mL of 2:1 acetonitrile-acetic acid is dissolved 315 mg (1.2 mmol) of tetramethylammonium-triacetoxyborohydride. The resulting solution is stirred for 1 at room temperature and cooled to −35° C., then 161 mg (0.15 mmol) of 40-O-[2-(t-butyldimethylsilyloxy)]ethyl-rapamycin is added. The resulting mixture is stirred at the same temperature overnight and is quenched by the addition of aq. sodium bicarbonate. The mixture is extracted with three portions of ethyl acetate. The organic solution is washed with aq. sodium bicarbonate, two portions of 30% aq. Rochelle's salt and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (40:60 hexane-ethyl acetate) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.06 (6H, s), 0.73 (1H, dd), 0.90 (9H, s), 1.64 (3H, s), 1.67 (3H, s), 3.02 (1H, m), 3.15 (1H, m), 3.64 (3H, m), 3.71 (2H, dd), 3.91 (1H, s); MS (FAB) m/z 1096 ([M+Na]$^+$), 1041 ([M-$HOCH_3$]$^+$), 1024 ([M-(OCH_3+H_2O)]$^+$), 1006 ([M-(OCH_3+2H_2O)]$^+$), 974 ([M-(OCH_3+CH_3OH+2H_2O)]$^+$).

MBA (rel. IC50)	3.9
IL-6 dep. prol. (rel. IC50)	53
MLR (rel. IC50)	18

Example 21: 28-O-Methyl-rapamycin

To a stirred solution of 103 mg (0.1 mmol) of 40-O-TBS-rapamycin (obtained by silylation of rapamycin with 1 eq. of TBS triflate in methylene chloride in the presence of 2 eq. of 2,6-lutidine at 0° C.) in 0.5 mL of methylene chloride is added 85.8 mg (0.40 mmol) of proton sponge followed by 44

mg (0.30 mmol) of trimethyloxonium tetrafluoroborate. The resulting brown heterogeneous mixture is stirred overnight, quenched with aq. sodium bicarbonate and extracted with ethyl acetate. The organic solution is washed with 1N HCl, aq. sodium bicarbonate and brine, then dried over anhydrous sodium sulfate, filtered and concentrated. The residue is purified by column chromatography on silica gel (60:40 hexane-ethyl acetate) to afford 40-O-t-butyldimethylsilyl-28-O-methyl-rapamycin. The latter compound is desilylated in the conditions described in example 10, step b) to afford, after PTLC (ethyl acetate), the title compound as a white solid: ^{1}H NMR ($CDCl_3$) δ0.70 (1H, dd), 1.68 (6H, 2s), 2.95 (1H, m), 3.13 (3H, s), 3.14 (3H, s), 3.28 (3H, s), 3.41 (3H, s); MS (FAB) m/z 950 ([M+Na]$^+$), 927 (M^+), 909 ([M-H_2O]$^+$), 896 ([M-OCH_3]$^+$), 878 ([M-(OCH_3+H_2O)]$^+$), 864 ([M-(OCH_3+CH_3OH)]$^+$), 846 ([M-(2CH_3OH+OH)]$^+$), 832 ([M-(OCH_3+2CH_3OH)]$^+$), 814 ([M-(3CH_3OH+OH)]$^+$).

MBA (rel. IC50)	1.58
IL-6 dep. prol. (rel. IC50)	1240
MLR (rel. IC50)	1300

Example 22: 40-O-(2-aminoethyl)-rapamycin

a) 40-O-(2-bromoethyl)-rapamycin

A solution of 914 mg rapamycin in 5 mL toluene containing 0.64 ml of 2,6-lutidine and 1.28 g of 2-bromoethyl triflate is heated at 65° C. for 18 h. The reaction mixture is then cooled to room temperature, poured on 20 ml of a saturated bicarbonate solution and extracted with 3×20 mL ethyl acetate. The organic phases are dried over sodium carbonate and the solvent removed at reduced pressure on the rotary evaporator. The residue is chromatographed on 100 g silica gel, eluting with hexane/ethyl acetate 3/2 to afford 40-O-(2-bromoethyl)-rapamycin as an amorphous solid: MS (FAB) m/z 1044 and 1042 (100%; M+Na); 972 and 970 (55%, M-(MeOH+H2O)).

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.45 (3H,s); 3.9 (4H, m); 4.78 (1H, s)

b) 40-O-(2-azidoethyl)-rapamycin

A solution of 2.4 g of 40-O-(2-bromoethyl)-rapamycin in 40 mL DMF is treated with 0.19 g sodium azide at room temperature. After 2 h, the mixture is poured on 100 mL of saturated sodium bicarbonate and extracted with 3×100 mL ethyl acetate. The organic phases are combined, dried over sodium sulfate and the solvent removed under reduced pressure. The crude product is purified by chromatography on silica gel eluting with hexane/ethyl to afford 40-O-(2-azidoethyl)-rapamycin: MS (FAB): 1005 (100%, M+Na); 951 (24%, M-MeOH); 933 (57%, M-(MeOH+H2O)

c) 40-O-(2-aminoethyl)-rapamycin

To a solution of 230 mg 40-O-(azidoethyl)-rapamycin in 3 mL of THF/water 5/1 at room temperature are added 307 mg of triphenylphosphine. The reaction mixture is becomes yellow. After 7 h, the reaction mixture is loaded on x g silica gel and chromatographed with ethyl acetate/methanol/acetic acid 50/50/0.5 to afford the title product in the form of its acetate: MS (FAB) m/z 979 (45%, M+Na); 957 (100% MH); 925 (63%, M-MeOH); 907 (25%, M-(MeOH+H2O)

MBA (rel. IC50): 0.7

IL-6 dep. prol. (rel. IC50): 10

Example 23: 40-O-(2-acetaminoethyl)-rapamycin

To a solution of 101 mg of the acetate of 40-O-(2-aminoethyl)-rapamycin in 2 mL THF are added 0.02 mL pyridine and 0.07 mL acetyl chloride. The reaction mixture is kept at room temperature for 18 h and then poured on 7 mL saturated sodium bicarbonate. The aqueous phase is extracted 3× with 5 mL ethyl acetate, the organic phases are combined and dried over sodium sulfate. The solvent is evaporated and the residue chromatographed on 10 g silica gel eluting first with ethyl acetate followed by ethyl acetate/methanol/acetic acid 50/50/0.5 to afford the title product: MS (FAB) m/z 1021 (20%, M+Na); 967 (28%, M-MeOH); 949 (100%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.71 (1H, q, J=12 Hz); 1.98 (3H, s); 3.13 (3H, s); 3.34 (3H, s); 3.44 (3H, s); 4.75 (1H, s)

MBA (rel. IC50): 1.1

IL-6 dep. prol. (rel. IC50): 2.3

Example 24: 40-O-(2-nicotinamidoethyl)-rapamycin

101 mg of 40-O-(2-aminoethyl)-rapamycin acetate are dissolved in 5 ml ethyl acetate and extracted 2× with saturated sodium bicarbonate. The organic phase is dried over sodium sulfate and the solvent evaporated. The residue is dissolved in 2 mL THF and treated with 22 mg DCC and 15 mg nicotinic acid. After 15 h at room temperature the reaction mixture is evaporated and the residue chromatographed on silica gel, eluting with ethyl acetate followed by ethyl acetate/methanol 9/1, to afford the title product: MS (FAB) m/z 1084 (80%, M+Na); 1062 (40%, MH); 1038 (100%, M-MeOH); 1012 (50%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.37 (3H, s); 7.39 (1H, dd); J=6 Hz, J=8 Hz), 8.19 (1H, d, J=8 Hz); 8.75 (1H, d, J=6 Hz); 9.04 (1H, broad s)

MBA (rel. IC50): 1.2

IL-6 dep. prol. (rel. IC50): 2.8

Example 25: 40-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin

To a solution of 30 mg N-methyl-imidazol-2-carboxylic acid in 1 mL DMF are added 58 mg DCC and 58 mg HOBT. After 2 h, 150 mg 40-O-(2-aminoethyl)-rapamycin are added and the reaction mixture is stirred for 18 at room temperature. The suspension is then filtered, the filtrate diluted with 5 mL ethyl acetate and washed with 2×2 mL of a saturated aqueous bicarbonate solution. The organic phase is dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue is chromatographed over 10 silica gel, eluting with hexane/ethyl acetate ¼ and then ethyl acetate to afford the title product:

MS (FAB) m/z 1087 (36%, M+Na); 1065 (57%, MH); 1033 (100%, M-MeOH); 1015 (46%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.72 (1H, q, J=12 Hz); 3.13 (3H, s); 3.33 (3H, s); 3.46 (3H, s); 4.03 (3H, s); 6.93 (1H, broad s); 6.98 (1H, broad s); 7.78 (1H, m);

MBA (rel. IC50): 1.1

IL-6 dep. prol. (rel. IC50): 7

Example 26: 40-O-(2-ethoxycarbonylaminoethyl)-rapamycin

A solution of 200 mg 40-O-(2-azidoethyl)-rapamycin in 3 mL THF/water 5/1 is treated with 267 mg triphenylphosphine for 7 h at room temperature. Then 0.4 mL pyridine are added followed by 194 µL ethyl chloroformiate. After 2 h, the reaction mixture is poured on 5 mL ethyl acetate and washed successively with 10 mL saturated sodium bicarbonate, 5 mL water and 5 ml 10% citric acid. The organic phase is dried over sodium sulfate and the solvent evaporated. The residue is chromatographed over 20 g silica gel, eluting with ethyl acetate followed by ethyl acetate/methanol 9/1, to afford the title product.: MS (FAB) m/z 1051 (35%, M+Na); 997 (30%, M-MeOH); 979 (100%, M-(MeOH+H2O)

H-NMR (CDCl3) d: 0.71 (1H, q, J=12 Hz); 1.24 (3H, t, J=8 Hz), 3.13 (3H, s); 3.34 (3H, s); 3.43 (3H, s); 4.10 (2H, q, J=8 Hz); (1H, m)

MBA (rel. IC50): 1.1
IL-6 dep. prol. (rel. IC50): 1.7

Example 27: 40-O-(2-tolylsulfonamidoethyl)-rapamycin

A solution of 200 mg 40-O-(2-aminoethyl)-rapamycin in 3 mL THF is treated with 0.4 mL pyridine and 390 mg tosyl chloride and the reaction mixture is stirred for 12 h at room temperature. The solution is then poured onto 5 ml of a saturated bicarbonate solution and the aqueous phase is extracted with 2×5 mL ethyl acetate. The combined organic phases are washed with 5 mL of 10% citric acid and 5 mL water. After drying on sodium sulfate the solvent is evaporated and the residue chromatographed on 20 g silica gel, eluting with hexane/ethyl acetate 1/1 to afford the title product as a white foam: MS (FAB) m/z 1133 (100%, M+Na); 1078 (25%, M-MeOH); 1061 (85%, M-(MeOH+H2O))

H-NMR (CDCL3) d: 0.68 (1H, q, J=12 Hz); 2,43 (3H, s); 3,13 (3H, s); 3,35 (3H, s); 3,41 (3H, s); 4.76 (1H, s); 5.85 (1H, t, J=6 Hz); 7.30 (2H, d, J=8 Hz); 7.75 (2H, d, J=8 Hz).

MBA (rel. IC50): 15.9
IL-6 dep. prol. (rel. IC50): 14

Example 28: 40-O-[2-(4',5'-dicarboethoxy-1',2',3'-triazol-1'-yl)-ethyl]-rapamycin

98 mg of 40-O-(2-azidoethyl)-rapamycin and 32 mg diethylacetylene dicarboxylate are suspended in 0.5 ml toluene and heated at 65° C. for 5 h. The reaction mixture is then cooled at room temperature, loaded on 10 g silica gel and eluted with hexane/ethyl acetate 1/1 to afford the title product: MS (FAB) m/z 1175 (20%, M+Na); 1121 (15%, M-MeOH); 1103 (60%, M-(MeOH+H2O))

H-NMR (CDCl3) d: 0.62 (1H, q, J=12 Hz); 1.40 (3H, t, J=8 Hz); 1.42 (3H, t, J=8 Hz); 3.13 (3H, s); 3.25 (3H, s); 3.33 (3H, s)

MBA (rel. IC50): 2.7
IL-6 dep. prol. (rel. IC50): 12

The previous examples may also be made using as starting material instead of rapamycin, 9-deoxo-rapamycin, 26-dihydro rapamycin, or 9-deoxo-, 26-dihydro-rapamycin. Alternatively, and preferably, as described e.g., in example 20, the rapamycin compounds of the above examples may be hydrogenated or reduced, using suitable protecting groups where necessary. The following novel methods for reducing the keto at C9, or hydrogenating the keto at C26 are provided:

Example 29: Removal of keto at C9

A stream of hydrogen sulfide is passed at room temperature through a stirred solution of 3.2 g (3.5 mmol) of rapamycin in 50 ml pyridine and 2.5 ml DMF. The solution turns from colorless to yellow. After two hours, the introduction of hydrogen sulfide is stopped and stirring is continued for five days, during which time the solution turns gradually orange. TLC and HPLC analysis verifies complete consumption of the starting material and the presence of a single new compound. The solution is purged with nitrogen for one hour and concentrated under reduced pressure. The residue is taken up in ethyl acetate, washed with cold 1N HCl solution (3×), saturated sodium bicarbonate solution and saturated brine. The organic layer is dried over anhydrous sodium sulfate and filtered and concentrated under reduced pressure. The residue is taken up in ether and precipitated sulfur is filtered off. Concentration of the ethereal solution followed by column chromatography on silica gel (10:4:1 CH_2Cl_2/i-Pr_2O/MeOH) yields 9-deoxorapamycin as a colorless foam. The identity of the product is confirmed by nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), and/or infrared spectrosopy (IR). 9-deoxorapamycin is found to exhibit the following characteristic physical data: ^{1}H NMR ($CDCl_3$) δ1.61 (3H,d,J=1 Hz, C17-CH_3), 1.76 (3H,d,J=1.2 Hz, C29-CH_3), 2.42 (1H,d,J=14.5 Hz, H-9), 2.74 (1H,d,J=14.5 Hz, H-9), 3.13 (3H,s,C16-OCH_3) 3.5 (3H,s,C27-OCH_3), 3.40 (3H,s,C39-OCH_3), 5.40 (1H,d,J=10 Hz, H-30), 5.57 (1H, dd,J_1=8.6 Hz, J_2=15 Hz, H-22), 5.96 (1H,d,J=9 Hz, H-18), 6.09 (1H,d,J=1.7 Hz, 10-OH), 6.15 (1H,dd,J_1=10 Hz, J_2=15 Hz, H-21), 6.37 (1H,dd,J_1=1.5 Hz, J_2=5 Hz, H-19), 6.38 (1H,J=9.5 Hz, H-20). ^{13}C NMR ($CDCl_3$) δ38.5 (C-9), 98.0 (C-10), 170.7 (C-1), 173.0 (C-8), 208.8 (C-32), 216.9 (C-26).

MS(FAB) m/z 922 8[M+Na^+]), 899 (M^+), 881 ([M-H_2O]$^+$), 868 ([M-OCH_3]$^+$), 850 ([M-(H_2O+OCH_3)]$^+$).

IR (major peaks)(cm^{-1}) 987, 1086, 1193, 1453, 1616, 1717, 1739, 3443.

MBA (rel. IC_{50}): 1
MLR (rel. IC_{50}): 14
IL-6 dep. prol. (rel. IC_{50}): 9

Example 30: Dihydrogenation of keto at C26

To a stirred solution of 421 mg (1.6 mmol) of tetramethylammonium triacetoxyborohydride in 2 ml of acetonitrile is added 2 ml of acetic acid. The resulting mixture is stirred for 30 minutes at room temperature and cooled to −35° C. At this temperature a solution of 180 mg (0.2 mmol) of 9-deoxo-rapamycin in 1 ml of acetonitrile is added and the resulting mixture is allowed to stir for 24 hours. The mixture is quenched with a saturated solution potassium tartrate solution and allowed to warm to room temperature. Stirring is continued until both layers are clear and ethyl acetate is added. The layers are separated and the aqueous layer is extracted twice with ethyl acetate. The resulting organic solution is washed once with a 10% sodium bicarbonate solution and twice with saturated brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue is purified by column chromatography on silica gel (90:10 AcOEt-hexane). As the starting material in this case was 9-deoxorapamycin, the final compound is 9-deoxorapamycin, 26-dihydrorapamycin is produced as a colorless foam, having the following characteristic spectroscopic data: ^{1}H NMR ($CDCl_3$) (major isomer) E0.9 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 0.93 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.00 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.07 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.17 (3H,d,J=6.9 Hz, CH$\underline{CH_3}$), 1.61 (3H,d,J=1 Hz, C17-CH_3), 1.73 (3H,d,J=1.2 Hz, C29-CH_3), 2.43 (1H,dd,J=4.1 and 16.0 Hz, H-33), 2.46 (1H,dd,J=13.8 Hz, H-9), 2.58 (1H,m,H-25), 2.77 (1H,dd,J=13.8 Hz, H-9), 2.82 (1H,dd,J=8.3 and 16.0 Hz, H-33), 3.17 (1H,dd,J=4.1 and 9.2 Hz, H-27), 3.61 (2H,m, H-14 and H28), 5.19 (1H,ddd,J=4.1, 4.6 and 8.3 Hz, H-34), 5.49 (1H, broad d,J=5.0 Hz, H-2), 5.56 (1H,d,J=9.1 Hz, H-30), 5.75 (1H,dd, J=6.9 and 14.7 Hz, H-22), 5.76 (1H,s,10-OH), 5.99 (1H, broad d,J=9.2 Hz, H-18), 6.10 (1H,m,H-21), 6.36 (2H,m,H-19 and H-20);

MS (FAB) m/z 924 ([M+Na]), 852 ([M-(H_2O+CH_3O)]$^+$).

MBA (rel. IC_{50}): 47
MLR (rel. IC_{50}): 134
IL-6 dep. prol. (rel. IC_{50}): 78

26-dihydrorapamycin is prepared in the same manner, using rapamycin in place of 9-deoxorapamycin. This product has the following characteristic spectroscopic data: ^{13}C-NMR ($CDCl_3$) (major isomer) d=208.3 (C-32); 194.0 (C-9); 169.3 (C-1); 166.6 (C-8); 140.9 (C-22); 136.5 (C-29); 136.2 (C-17); 133.5 (C-20); 129.1 (C-21); 128.7 (C-18); 126.2 (C-30); 125.3 (C-19); 98.6 (C-10); 84.4 (C-39); 83.9 (C-16; 81.6 (C-27); 75.4 (C-34); 74.3 (C-28); 73.9 (C-40); 72.9 (C-26); 67.4 (C-14); 59.1 (27-O$\underline{CH_3}$); 56.6 (39-O$\underline{CH_3}$); 55.9 (16-O$\underline{CH_3}$); 51.3 (C-2); 46.8 (C-31); 44.3 (C-6); 40.4

(C-33); 40.4 (C-25); 39.5 (C-24); 38.8 (C-15); 38.0 (C-36); 34.3 (C-23); 34.2 (C-38); 33.5 (C-11); 33.3 (C-37); 33.2 (C-35); 31.5 (C-42); 31.3 (C-41); 30.9 (C-13); 27.1 (C-12); 27.0 (C-3); 25.2 (C-5); 21.4 (23-$\underline{C}H_3$); 20.7 (C-4); 17.3 (11-$\underline{C}H_3$); 16.1 (31-$\underline{C}H3$); 15.9 (35-$\underline{C}H_3$); 14.4 (25-$\underline{C}H_3$); 14.2 (29-$\underline{C}H_3$); 10.3 (17-$\underline{C}H_3$).

MS (FAB) m/z: 884 (M-OCH_3, 35%); 866 (M-[OCH_3+H_2O], 100%; 848 (M-[OCH_3+2 H_2O], 40%).

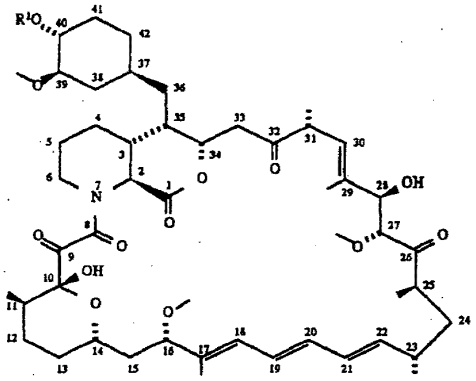
MBA (rel. IC_{50}): 1.7

MLR (rel. IC_{50}): 1

IL-6 dep. prol. (rel. IC_{50}): 7.5

We claim:

1. A compound of the formula



wherein R^1 is hydroxy(C_{1-6})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

2. A compound according to claim 1 in which R^1 is hydroxy(C_{1-3})alkyl or hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

3. A compound according to claim 1 in which R^1 is hydroxy(C_{1-3})alkyl.

4. A compound according to claim 1 in which R^1 is hydroxy(C_{1-3})alkoxy(C_{1-3})alkyl.

5. The compound according to claim 1 which is 40-O-(3-hydroxypropyl)-rapamycin.

6. The compound according to claim 1 which is 40-O-[2-(2-hydroxyethoxy)ethyl]-rapamycin.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier therefor.

8. A method of inducing an immunosuppressant effect in a subject in need of immunosuppression, which comprises administering to said subject an immunosuppressant effective amount of a compound according to claim 1.

9. A method of preventing allograft rejection in a subject in need of such treatment, which comprises administering to said subject a compound according to claim 1 in an amount effective to prevent allograph rejection.

10. The compound according to claim 1 which is 40-O-(3-hydroxyethyl)-rapamycin.

* * * * *

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