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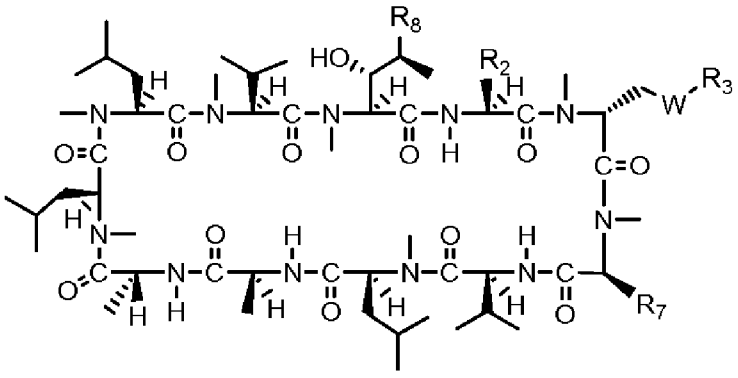
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(54) **Title**: NOVEL CYCLOSPORIN DERIVATIVES AND USES THEREOF



(I)

(57) **Abstract**: The present invention relates to a compound of the Formula (I)): or pharmaceutically acceptable salt thereof, wherein the symbols are as defined in the specification; a pharmaceutical composition comprising the same, a method for treating or preventing viral infections, inflammation, dry eye, central nervous disorders, cardiovascular diseases, cancer, obesity, diabetes, muscular dystrophy, and hair loss.

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NOVEL CYCLOSPORIN DERIVATIVES AND USES THEREOF

Cross Reference To Related Applications

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 61/793,917 filed March 15, 2013; the entire contents of which is incorporated herein by reference in its entirety.

Field of the Invention

[0002] The invention relates to novel cyclosporine derivatives, their pharmaceutical compositions comprising the same, and methods for treating or preventing viral infections, inflammation, dry eye, central nervous disorders, cardiovascular diseases, cancer, obesity, diabetes, muscular dystrophy, and hair loss.

Background of the Invention

[0003] Cyclosporins in nature are poly-N-methyl, cyclic undecapeptides, isolated from fungi. Cyclosporin A has an immunosuppressive activity and has been used for more than 30 years to prevent rejection in kidney, heart and liver transplant recipients. It possesses anti-inflammatory properties and has been used for treating severe rheumatoid arthritis, severe psoriasis, Behget's uveitis, and dry eye disease. In addition, it is useful for treating severe ulcerative colitis, Crohn's disease, alopecia areata, aplastic anemia, HSV-1 stromal keratitis, systemic lupus erythematosus, and severe lupus nephritis. However, its strong immunosuppressive activity limits its applications in many diseases.

[0004] The anti-HIV activity of cyclosporin A was first discovered in 1986 and has been continually studied since then (Klatzmann, D., *et al.*, 1986, *C R Acad. Sci. III*, 303(9):343-8; Wainberg, M. A., *et al.*, 1988, *Blood,* 72, 1904-10; Luban, J., *et al.*, 1993, *Cell*, 73, 1067–1078; each of which is incorporated herein by reference). Its non-immunosuppressive derivative, NIM-811, was reported to have potent anti HIV activity due to its ability to inhibit cyclophilin A (Franke, E. K., *et al.*, 1994, *Nature*, 372, 359–362; Thali, M., *et al.*, 1994, *Nature*, 372, 363–365; Gamble, T. R., *et al.*, 1996, *Cell*, 87, 1157–1159; Rosenwirth B., *et al.*, 1994, *Antimicrob. Agents Chemother.*, 38, 1763–1772; each of which is incorporated herein by reference).

[0005] Cyclosporin A and its non-immunosuppressive derivatives, as such as NIM-811 (N-MeIle-4-Cyclosporin), Debio-025, and SCY-635, bind and inhibit cyclophilins; cyclophilins interact with HCV protein NS5A and NS5B and stimulate its RNA-binding activity. As a result, these compounds have an effective anti-HCV activity (Watashi, K., *et*

al., 2007, *Rev. Med. Virol.,* 17:245–252.37; Inoue, K., *et al.*, 2001, *Nippon Rinsho.*, 59, 1326-30; Inoue, K., *et al.*, 2003, *J. Gastroenterol.*, 38, 567-72; Watashi, K., *et al.*, 2003, *Hepatology*, 38, 1282-8; Gaither, L. A., et al., 2010, *Virology*, 397, 43-55; each of which is incorporated herein by reference). Currently, NIM-811, Debio-025, and SCY-635 are undergoing clinical trials for treating HCV.

[0006] NIM-811 and Debio-025 have a chemical structure similar to cyclosporine A and possess a poor pharmacokinetic profile. In addition, they are metabolized by P450 for inducing drug interactions (Lill, J., *et al.*, 2000, *Am J Health-Syst Pharm* 57, 1579; incorporated herein by reference).

[0007] SCY-635 has an improved pharmacokinetic profile and low blood serum binding. In addition, it has a low potential for drug-drug interactions. SCY-635's *in vitro* anti-HCV activity (EC_{50}) was reported to be 0.10 μM (Hopkins, S. *et al.*, 2010, *Antimicrob. Agents Chemother.*, 54, 660-672, incorporated herein by reference). However, SCY-635 is not chemically stable, as it is easily converted to its diastereoisomer by epimerization. Its diasteroisomer is expected to have poor binding activity with cyclophilins, and as a result, its anti-viral activity *in vivo* may be affected (See, e.g., WO2012/009715, WO2012/021796, and WO2012/075494, each of which incorporated herein by reference in its entirety).

[0008] Cyclosporin A and its non-immunosuppressive derivatives were also found to possess anti-HBV activity through the inhibition of cyclophilins (Chokshi, S., *et al.*, 2012, Gut 61:A11; Chokshi, S., *et al.*, 2012, Poster Presentations, 47th Annual Meeting of the European Association for the Study of the Liver (EASL 2012), Barcelona, Spain; Chokshi, S., *et al.*, 2011, Abstract 190 (Poster Presentations), 46th Annual Meeting of the European Association for the Study of the Liver (EASL 2011), Berlin, March 30-April 3; Tian, X. C., *et al.*, 2010, *J. Virol.,* 84, 3373–3381; Xia, W. L., *et al.*, 2004, *Hepatobiliary Pancreat Dis Int.,* 4, 18-22; Michael, J., *et al.*, 2003, *J. Virol.*, 77, 7713–7719; each of which is incorporated herein by reference). Recently, sodium taurocholate cotransporting polypeptide (NTCP) was identified as an HBV and HDV entry receptor for viral infectivity, the pre-S1 domain of HBV large envelope protein is a key determinant for receptor binding and then for viral entry (Yan, H., *et al.*, 2012, *eLife*, 1, e00049; Chen, Z. J., *et al.*, 2012, *eLife*, 1, e00301; Yan, H., *et al.*, 2013, *J. Virol.*, 87, 7977; Ni, Y., *et al*, 2013, *Gastroenterology*. 2013 Dec 19. pii: S0016-5085(13)01808-8. doi: 10.1053/j.gastro.2013.12.024; Chen, P. J., *et al.,* 2013, *Cell & Bioscience,* 3: 2; Iwamoto,

M., *et al.*, 2014, *Biochem Biophys Res Commun.*, 443, 808; Yan, H., *et al.*, 2014, *J. Virol.*, 88, 3273; each of which is incorporated herein by reference). In addition, pharmacological studies suggest that NTCP may serve as a therapeutic drug target (Tsukuda, S., *et al.*, 2014, *Clin. Res. Infect. Dis.,* 1(1): 1004; Watashi, K. *et al.*, 2014, *Int. J. Mol. Sci.,* 15, 2892; each of which is incorporated herein by reference). Cyclosporin A and its analogs can inhibit NTCP and therefore inhibit HBV entry, which results in potent anti-HBV activity (Nkongolo, S., *et al.*, *J Hepatol.* 2013 Dec 1. pii: S0168-8278(13)00824-6. doi: 10.1016/j.jhep.2013.11.022; Watashi, K., *et al.*, *Hepatology*, 2013 Dec 21. doi: 10.1002/hep.26982; each of which is incorporated herein by reference). This anti-viral mechanism of cyclosporin A and its non-immunosuppressive analogs is independent to cyclophilin binding or calcineurin binding.

[0009] Furthermore, cyclophilins were reported to regulate the life cycle and pathogenesis of several viruses, including severe acute respiratory syndrome coronavirus, vaccinia virus, and herpes simplex virus (Castro, A. P., *et al.*, 2003, *J. Virol.,* 77, 9052–9068; Chen, Z., L., *et al.*, 2005, *J. Infect. Dis.* 191(5):755-760; Arai, C., et al., *Nihon Rinsho Meneki Gakkai* Kaishi., 35(1), 87-91; Labetoulle, M., 2012, *J Fr Ophtalmol.*, 35(4), 292-307; De Clercq, E., 2008, *Expert Opin Emerg Drugs.*, 13(3):393-416; Vahlne, A., 1992, *Arch Virol.*, 122(1-2):61-75; each of which is incorporated herein by reference). Cyclosporin A and its non-immunosuppressive derivatives also possess such anti viral-activities.

[0010] N-MeVal-4-Cyclosporin (SDZ 220-384), another non-immunosuppressive cyclosporine derivative, was reported to have similar biological activities to that of NIM-811 (Fliri, H., *et al.*, 1993, *Ann. N Y Acad Sci.* 696, 47-53; Zenke, G., *et al.,* 1993, *Ann N Y Acad Sci.* 23;685:330-5).

[0011] Hepatitis C virus (HCV) is a small (55-65 nm in size), enveloped, positive sense single strand RNA virus in the Flaviviridae family. HCV has a high rate of replication and an exceptionally high mutation rate. About 80% of people infected with HCV develop chronic, persistent infection. More than 4 million Americans have been infected with HCV and more than 200 million people are estimated to be infected chronically worldwide. About 35,000 new cases of hepatitis C are estimated to occur in the United States each year. HCV infection is responsible for about 50% of all chronic liver disease, 30% of all liver transplants, and 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The peg-interferon and ribavirin combination is the standard treatment for chronic

hepatitis C, but it has low efficacy against HCV infection. Recently, the FDA has approved Vertex's Incivek (telaprevir) and Merck's Victrelis (boceprevir) as an add-on to the current interferon/ribavirin therapy for treating HCV. Both drugs are HCV protease inhibitors that target the virus to prevent its replication. However, due to HCV's fast mutation rate, drug resistance can be developed in a short period of time. Thus, there exists a need for an effective therapeutic for HCV treatment.

[0012] Hepatitis B virus (HBV) is a 42 nm partially double stranded DNA virus composed of a 27 nm nucleocapsid core (HBcAg) that is surrounded by an outer lipoprotein envelope containing the surface antigen (HBsAg). More than 2 billion people have been infected, and there are 350 million chronic carriers of the virus. The disease has caused epidemics in parts of Asia and Africa. Chronic hepatitis B will cause liver cirrhosis and liver cancer, a fatal disease with a very poor response to current chemotherapies. The infection is preventable by vaccination, and HBV load and replication can be reduced by current antiviral drugs, such as lamivudine (Epivir), adefovir (Hepsera), tenofovir (Viread), telbivudine (Tyzeka), entecavir (Baraclude), and the two immune system modulators interferon alpha-2a and PEGylated interferon alpha-2a (Pegasys). However, none of the available drugs can clear the infection. There remains a need for an effective therapeutic to treat HBV infection.

[0013] The non-immunosuppressive cyclosporin derivatives bind to cyclophilins, a family of host proteins that catalyze *cis-trans* peptidyl-prolyl isomerization in protein folding and regulation, which are crucial for the processing and maturation of the viral proteins for viral replication. HIV and HCV are viruses with a high mutation rate. All current anti-viral drugs target the virus itself; when the virus mutates, it leads to the development of drug resistance. Instead of directly targeting the virus, targeting host cofactors (cyclophilins) will be slow down the development of drug resistance due to a higher genetic barrier (Rosenwirth, B., *et al.*, 1994, *Antimicrob. Agents Chemother.*, 38, 1763–1772; Tang, H. L. *et al.*, 2010, *Viruses*, 2, 1621-1634; Hopkins, S. *et al.*, 2010, Oral Presentation, Scynexis's SCY-635 Demonstrates Impressive Barrier to Resistance in HCV Treatment, the 45th Annual Meeting of the European Association for the Study of the Liver (EASL 2010), Vienna, Austria, April 14-18; each of which is incorporated herein by reference). Cyclosporine derivatives affect a new target, cyclophilins, and therefore represent a new mechanism of action against viruses.

[0014] There are 17 cyclophilins in the human genome, but the functions of these cyclophilin isoforms are still unclear (Davis, T. L., et al., 2010, *PLoS Biol.* 8(7):e1000439; incorporated herein by reference). Cyclophilin A, B, C, D, and other such isoforms play an important role in the pathophysiology of a number of serious diseases, such as cancer (Campa, MJ., et al., 2003, Cancer Res., 63(7), 1652-6; Li, M., et al., 2006, *Cancer*, 106: 2284-94; Yang, H., et al., 2007, *Biochem Biophys Res Commun.*, 361(3):763-7; Obchoei, S., et al., 2009, *Med Sci Monit.*, 15(11), RA221-32; Andersson, Y., et al., 2009, *Br J Cancer*, 101, 1307-1315; Lee, J., 2010, *Arch Pharm Res.*, 33(2), 181-7; Lee, J., et al., 2010, J Exp Clin Cancer Res., 29:97; Obchoei, S., 2011, *Molecular Cancer*, 10:102; Takahashi, M., et al., 2012, *Oncol Rep.*, 27(1):198-203; Qian, Z., et al., 2010, *BMC Cancer*, 12:442; each of which is incorporated herein by reference), inflammations (the result of interactions between a secreted extracellular cyclophilin and CD-147, a surface protein; Yurchenko V., 2005, *Immunology*, 117(3):301-9; Yurchenko, V., 2010, *Clin Exp Immunol.*, 160(3):305-17; Malesević, M., 2010, *Angew Chem Int Ed Engl.*, 49(1):213-5; each of which is incorporated herein by reference), rheumatoid arthritis (Wells, G., et al., 2000, Cochrane Database Syst Rev., (2):CD001083; Kim, H., et al., 2005, *Clin Immunol.*, 116(3):217-24; Yang, Y., *Rheumatology (Oxford)*, 47(9):1299-310; Yurchenko, V., et al., 2006, *Immunology*, 117(3):301-9; Damsker, J. M., 2009, Immunology, 126(1):55-62; Wang, L., et al., 2010, *J Clin Immunol.*, 30(1):24-33; Billich A., et al., 1997, *J Exp Med.*, 185:975-80; De Ceuninck F., et al., 2003, *Arthritis Rheum.*, 48:2197-206; each of which is incorporated herein by reference), respiratory inflammation (Foda, H. D., et al., 2001, *Am J Respir Cell Mol Biol.*, 25:717-24; Hasaneen, N. A., et al., *FASEB J.*, 19:1507-9.Yurchenko, V., et al., 2006, *Immunology*, 117(3):301-9; Gwinn, W. M., 2006, *J Immunol.*, 177(7):4870-9; Onoue, S., 2009, *J Control Release.*, 138(1):16-23; Balsley, M. A., et al., 2010, *J Immunol.*, 185(12):7663-70; Balsley, M., et al., 2010, *Am. J. Respir. Crit. Care Med.*, 181(1): A6821; Stemmy, E. J., et al., 2011, J. Asthma, 48(10):986-993; Stemmy, E. J., et al., 2011, *Am J Respir Cell Mol Biol.*, 45(5):991-8; Amin, K., 2012, *Respir Med.*, 106(1):9-14; Onoue, S., 2012, *Eur J Pharm Biopharm.*, 80(1):54-60; each of which is incorporated herein by reference), lupus (Caccavo, D., et al., 1997, Arthritis & Rheumatism, 40(1):27–35; Dostál, C., et al., 1998, *Lupus*, 7(1):1 29-36; Tam, LS., et al., 1998, *Q J Med.*, 91(8):573-580; Fu, LW., et al., 1998, Rheumatology 37 (2): 217-221; Hallegua, D., et al., 2009, *Lupus*, 9: 241-251; each of which is incorporated herein by reference), psoriasis (Ellis, C. N., 1991, *N Engl J Med.*, 324, 277-284; Lebwohl, M., et al., 1998, J Am Acad Dermatol., 39(3):464-75;

Rosmarin, DM., et al., 2010, J Am Acad Dermatol., 62(5):838-53; each of which is incorporated herein by reference), atopic dermatitis (Naeyaert, J. M., et al., 1999, *Dermatology*, 198:145–152; Pacor, ML., et al., 2001, *Recenti Prog Med.*, 92(6):390-1; Ricci, G., et al., 2009, *Drugs*, 69(3):297-306; Simon, D., 2011, *Curr Probl Dermatol.*, 41:156-64; each of which is incorporated herein by reference), dry eye disease (Pflugfelder, S. C., 2004, *Am J Ophthalmol.*, 137(2), 337-42; Kymionis, G. D., et al 2008, *Clin Ophthalmol.*, 2, 829-836; Kunert, K. S., et al., 2002, *Arch Ophthalmol.*, 120, 330-7; Yavuz, B., et al., 2012, *Scientific World Journal*. 2012:194848.; each of which is incorporated herein by reference), severe Graves' ophthalmopathy (Prummel, M. F., 1989, *N Engl J Med.*, 321(20), 1353-9; incorporated herein by reference), endogenous uveitis (Nussenblatt, R. B., et al., 1991, *Am J Ophthalmol.*, 112(2), 138-46; which is incorporated herein by reference), Wegener's granulomatosis (Georganas, C., et al., 1996, *Clin Rheumatol.*, 15(2), 189-92; incorporated herein by reference), vernal keratoconjutivitis (Pucci, N., et al., 2002, *Ann Allergy Asthma Immunol.*, 89, 298-303; incorporated herein by reference), atopic keratoconjutivitis (Akpek, E. K., et al., 2004, *Ophthalmology*, 111, 476-82; incorporated herein by reference), ligneous conjutivitis (Rubin, B. I., et al., 1991, *Am J Ophthalmol.*, 112, 95-96; incorporated herein by reference), conjuctival linchen planus (Levell, N. J., et al., 1992, *Br J Dermatol.*, 127, 66-7; incorporated herein by reference), and superior limbic keratoconjutivitis (Perry, H. D., et al., 2003, *Ophthalmology*, 110, 1578-81; incorporated herein by reference), inflammatory bowel disease-Crohn's Disease and Ulcerative Colitis (Sandborn, W. J., 1995, *Inflamm Bowel Dis*. 1:48-63; Shibolet, O., et al., 2005, *Cochrane Database Syst Rev.*, (1):CD004277; Rufo, P. A., et al., 2006, *Paediatr Drugs*, 8(5):279-302; Reindl, W., et al., 2007, *Gut.*, 56(7):1019; Hart, A. L., et al., 2010, *Aliment Pharmacol Ther.*, 32(5):615-27; Cheifetz, A. S., et al., 2011, *J Clin Gastroenterol.*, 45(2):107-12; Sharkey, L., 2011, *J Crohns Colitis.*, 5(2):91-4; Fabro, M., et al., 2011, *Curr Drug Targets.*, 12(10):1448-53; Van Assche, G., et al., 2011, *Gut.*, 60(1):130-3; each of which is incorporated herein by reference), NSAID-induced enteropathy (LoGuidice, A., at al., 2010, *Toxicol. Sci.*, 118, 276-285; which is incorporated herein by reference), cardiovascular diseases (including vascular stenosis, atherosclerosis, abdominal aortic aneurysms, aortic rupture, cardiac hypertrophy, pulmonary arterial hypertension, myocarditis and myocardial fibrosis, and ischaemic heart diseases; Jin, Z. G., et al., 2000, *Circ Res.*, 87(9):789-96; Yurchenko, V., et al., 2005, Immunology, 117, 301-309; Suzuki, J., et al., 2006, *Circ Res.*, 98(6):811-7; Satoh, K., et al., 2008, *Circulation.*, 117(24):3088-

98; Nishihara, M., et al., 2008, *J Mol Cell Cardiol.*, 44(2):441-442; Satoh, K., et al., 2010, *Circ J.*, 74(11):2249-56; Satoh, K., et al., 2010, *Antioxid Redox Signal.*, 12(5):675-82; Hausenloy, D. J., et al., 2012, *Br J Pharmacol.* 165(5):1235-45; Coppinger, J. A., et al., 2004, *Blood*, 103(6):2096-104; Satoh, K., et al., 2010, *Antioxid Redox Signal.*, 1:12(5), 675-682; Nigro, P., et al., 2010, *J Exp Med.*, 208(1):53-66; Wang, W. L., et al., 2011, *Med Hypotheses,* 77(5):734-8; Hattori, F., 2012, *J Mol Cell Cardiol.*, 53(1):1-2; Seizer P., 2012, *J Mol Cell Cardiol.*, 53(1):6-14; each of which is incorporated herein by reference), and ischaemic brain diseases (Boulos, S., et al., 2007, *Neurobiol Dis.*, 25:54-64; incorporated herein by reference).

[0015] Due to cyclophilin inhibition, cyclosporin derivatives also possess the following biological activities: anti-fungal (Kirkland, T. N., et al., 1983, *Antimicrob Agents Chemother.*, 24(6): 921–924**;** Mody, C. H., et al., 1988, *Infect Immun.*, 56(1): 7–12; Roilides, E., et al., 1994, *Antimicrob Agents Chemother.*, 38(12): 2883–2888; Moussaïf, M., et al., 1997, *Appl Environ Microbiol.*, 63(5):1739-43; Cruz, M. C., et al., 2000, *Antimicrob Agents Chemother.*, 44(1):143-9; each of which is incorporated herein by reference), anti-malarial (Nickell, S. P., et al., 1982, *Infect Immun.*, 37(3):1093-100; Murphy, J. R., et al, 1988, *Antimicrob Agents Chemother.*, 32(4):462-6; Marín-Menéndez, A., et al., 2012, *Mol Biochem Parasitol.*, 184(1):44-7; each of which is incorporated herein by reference), and anti-parasitic (including Leishmania donovani, Cryptosporidium parvum, Hymenolepis nana, Toxoplasma, Trypanosoma cruzi, and Schistosome; Chappell, L. H., et al., 1992, *Parasitology*, 105 Suppl:S25-40; Bell, A., et al., 1996*, Gen Pharmacol.*, 27(6):963-71; Yau, W. L., et al., 2010, *PLoS Negl Trop Dis.*, 4(6):e729; Yurchenko, V., et al., 2008, *Int J Parasitol.*, 38(6):633-9; Perkins, M. E., et al., 1998, *Antimicrob Agents Chemother.*, 42(4):843-8; Matsuzawa, K., et al., 1998, *Int J Parasitol.*, 28(4):579-88; Silverman, J. A., et al., 1997, *Antimicrob Agents Chemother.*, 41(9):1859-66; Búa, J., et al., 2008, *Parasitology*, 135(2):217-28; Búa, J., et al., 2004, *Bioorg Med Chem Lett.*, 14(18):4633-7; Bout, D. T, et al., 1984, *Am J Trop Med Hyg.*, 33(1):185-6; Bout, D., et al., 1986, *Infect Immun.*, 52(3):823-7; Munro, G. H., et al., 1991, *Parasitology*, 102 Pt 1:57-63; each of which is incorporated herein by reference). In addition, cyclosporin derivatives can promote hair growth (Watanabe, S., et al., 1991, J Dermatol., (12):714-9; Paus R., et al., 1994, *J Invest Dermatol.*, 103:2, 143-7; Hozumi, Y., et al., 1994, J Dermatol Sci., 7 Suppl:, S33-8; Takahashi, T., et al., 2001, *J Invest Dermatol.*, 117(3):605-11; Taylor M., et al.,

1993, *J Invest Dermatol.*, 100:3, 237-9; Gafter-Gvili, A., et al., 2004, *Arch Dermatol Res.*, 296(6):265-9; each of which is incorporated herein by reference).

[0016] Recent research for Alzheimer's disease indicated that Cyclophilin A is a key target for treating APOE4-mediated neurovascular injury and the resulting neuronal dysfunction and degeneration (Bell, R. D., et al., 2012, Nature, 485(7399):512-6; Bell, R. D., et al., 2009, *Acta Neuropathol.*, 118(1):103-13; each of which is incorporated herein by reference).

[0017] Due to the function of extracellular cyclophilins, it is necessary to emphasize that the special target of a secreted extracellular cyclophilin using a cell-impermeable derivative of cyclosporine will be very effective in reducing inflammation for diseases such as respiratory inflammation and cardiovascular diseases (Yurchenko V., 2005, *Immunology*, 117(3):301-9; Yurchenko, V., 2010, *Clin Exp Immunol.*, 160(3):305-17; Malesević, M., 2010, *Angew Chem Int Ed Engl.*, 49(1):213-5; Balsley, M. A., et al., 2010, *J Immunol.*, 185(12):7663-70; Balsley, M., et al., 2010, *Am. J. Respir. Crit. Care Med.*, 181(1): A6821; Satoh, K., et al., 2010, *Circ J.*, 74(11):2249-56; each of which is incorporated herein by reference).

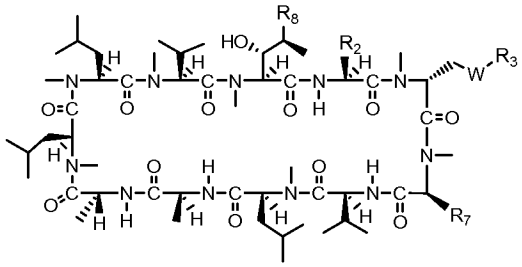
[0018] Cyclophilin D (CypD) is very important for mitochondrial related neuro and cardiovascular functions because it is an integral part of the mitochondrial permeability transition pore (mPTP). Unregulated opening of the mPTP can lead to mitochondrial swelling and cell death. Thus, the CypD-mediated mPTP is directly linked to a new pharmacologic treatment strategy for many neuro and cardiovascular diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, aging, heart failure, traumatic brain injury, spinal cord injury, epilepticus, stroke, ischemia-reperfusion injury in the brain, heart, kidney, and particularly in myocardial infarction. The CypD-mediated mPTP is also linked to a new treatment strategy for cancer, obesity, diabetes, and muscular dystrophy (Henry-Mowatt, J., 2004, *Oncogene*, 23, 2850-60; Galluzzi, L., 2006, *Oncogene*, 25, 4812-4830; Hirai, K., et al., 2001, *J Neurosci.*, 21, 3017-3023; Friberg, H., et al., 2002, *Biochimie*, 84, 241-250; Waldmeier, P. C., et al., 2003, *Curr Med Chem.*, 10, 1485-506; Hansson, M. J., et al., 2004, *J Bioenerg Biomembr.*, 36, 407-13; Sullivan, P. G., et al., 2005, *J Neurosci Res.,* 79, 231-9; Baines, C. P., et al, 2005, *Nature* 434, 658-662; Shanmuganathan, S., et al, 2005, *Am J Physiol Heart Circ Physiol.*, 289, H237–H242; McBride, H. M., et al., 2006, *Curr Biol.*, 16, R551–560; Mandemakers, W., et al., 2007, *J Cell Sci.,* 120, 1707-1716; Kroemer, G., et al., 2007, *Physiol Rev.*, 87, 99-163; Ibarra, A., et

al., 2007, *Brain Res.*, 1149, 200-209; Michelakis, E. D., et al, 2008, *Circulation*, 117, 2431-2434; Du, H., et al, 2008, *Nature Medicine,* 14, 1097-1105; Piot C., et al., 2008, *N Engl J Med.*, 359, 473-81; Hatton, J., et al., 2008, *J Neurosurg.*, 109, 699-707; Tatsuta, T., et al., 2008, *EMBO J*, 27, 306-314; Reutenauer, J., et al., 2008, *Br J Pharmacol.*, 155, 574-84; Mazzeo, A. T., et al., 2009, *Exp Neurol.*, 218, 363-370; Galluzzi, L., et al, 2009, *Nature Rev Neurosci.*, 10, 481-494; Halestrap, A. P., et al., 2009, *Biochim Biophys Acta.*, 1787, 1402-15; Arnett, A. L. H., et al., 2009, *Curr. Opin. Genet. Dev.*, 19, 290-297; Tiepolo, T., et al., 2009, *Br J Pharmacol.*, 157, 1045–1052; Wissing, E. R., et al., 2010, *Neuromuscul Disord.*, 20, 753-60; Halestrap, A. P., et al., 2010, *Biochem Soc Trans.*, 38, 841-860; Cernak, I., et al., 2010, *J Cereb Blood Flow Metab.*, 30, 255-66; Elrod, J. W., et al., 2010, *J Clin Invest.*, 120, 3680–3687; Duchen, M. R., et al., 2010, *Essays Biochem.*, 47, 115-37; Schapira, A. H. V., et al., 2011, Parkinson's Disease, Volume 2011, 1-7 Article ID 159160; Osman, M. M., et al., 2011, *Neuropeptides*, 45, 359-368; Devalaraja-Narashimha K., et al., 2011, *FEBS Lett.*, 585, 677-82; Fujimoto, K., et al., 2010, *Proc Natl Acad Sci U S A.* 107, 10214-9; Irwin, W. A., et al., 2003, *Nat Genet.*, 35, 267-271; Angelin, A., et al., 2007, *Proc Natl Acad Sci U S A*, 104, 991-6; Merlini, L., et al., 2008, *Proc Natl Acad Sci U S A*, 105, 5225-9; Millay, D. P., 2008, *Nat Med.*, 14, 442-7; each of which is incorporated herein by reference). Cyclosporine A and its derivatives can block CypD to prevent mitochondrial swelling and cell death, and therefore could be useful for treatment of the aforementioned diseases, for example, as a neuro and cardiovascular protective agent or as a novel mitochondrial medicine.

[0019] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Summary of the Invention

[0020] In one aspect, the present invention provides a compound of Formula (I):



(I)

or pharmaceutically acceptable salt thereof, wherein:

R_8 is n-butyl, (*E*)-but-2-enyl,  , $-(CH_2)_4-SR_9$, $-(CH_2)_4-(C=O)OR_9$, or $-(CH_2)_3-(C=O)OR_9$;

each occurrence of R_9 is independently hydrogen or (C_1-C_6)alkyl;

R_2 is ethyl, 1-hydroxyethyl, isopropyl or n-propyl;

W is O, S, CH_2, or NR_1;;

R_1 is hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1-C_6)$alkyl, $-C(=O)O(C_1-C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of (C_1-C_6)alkyl, phenyl and benzyl;

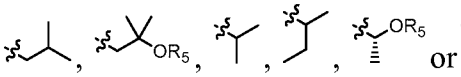
R_3 is:

H;

$(C_7\text{-}C_{12})$alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

$(C_7\text{-}C_{12})$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_7\text{-}C_{12})$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

R_7 is  ;

R_5 is:

H;

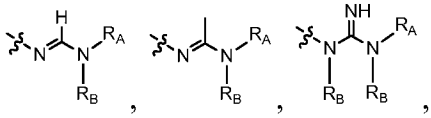
$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2\text{-}C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from hydroxy, $(C_1\text{-}C_6)$alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2\text{-}C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3\text{-}C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, $(C_3\text{-}C_7)$cycloalkyl, aryl (e.g., phenyl), OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1\text{-}C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  ,

$NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl (e.g., phenyl), $S(C_1\text{-}C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

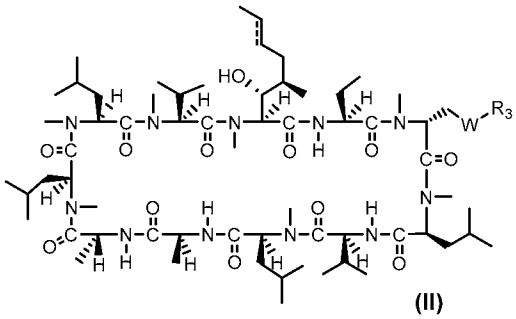
or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

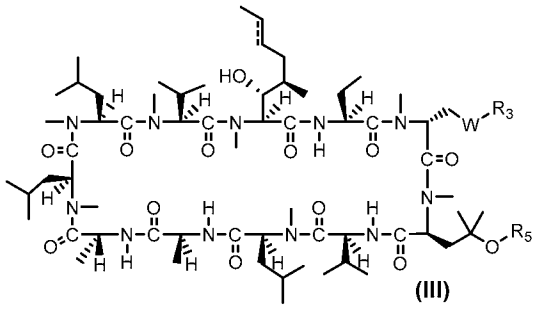
p is an integer of 0, 1, 2, 3, 4, or 5; and

m is an integer of 1, 2, 3, 4 or 5.

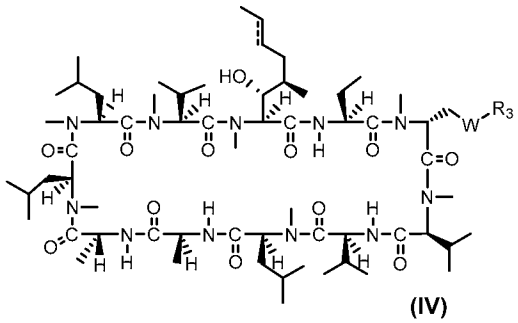
[0021] In another aspect, the present invention provides a compound of Formulae (II) through (VI):



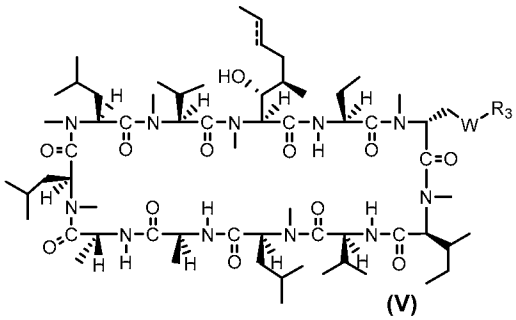
(II)



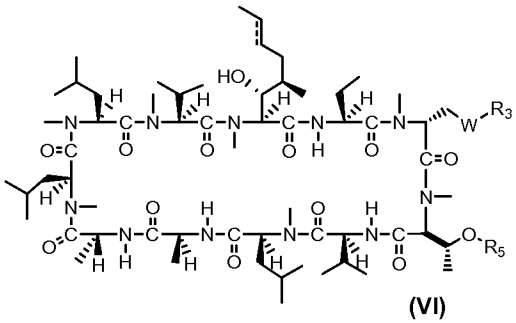
(III)



(IV)



(V)



(VI)

,

or pharmaceutically acceptable salt thereof, wherein:

┇ represents a single bond or double bond;

each W is independently O, S, or NR_1;

each R_1 is independently hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O(C_1-C_6)alkyl, -C(=O)O(C_1-C_6)alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of (C_1-C_6)alkyl, phenyl and benzyl;

each R_3 is independently:

H;

(C_7-C_{12})alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

(C_7-C_{12})alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$; or

(C_7-C_{12})alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

each R_5 is independently:

H;

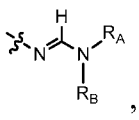
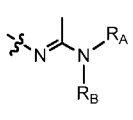
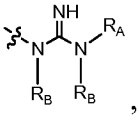
$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2\text{-}C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2\text{-}C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3\text{-}C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, $(C_3\text{-}C_7)$cycloalkyl, aryl (e.g., phenyl), OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1\text{-}C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  ,  ,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl (e.g., phenyl), $S(C_1\text{-}C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O$(C_1$-$C_6)$alkyl, -C(=O)O$(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

or R_A and R_B, together with the nitrogen atom to which they are attached, form -N=CH-$NR_FR_{F'}$, -N=CMe-$NR_FR_{F'}$, or -$NR_FC(=NH)NR_FR_{F'}$;

each occurrence of R_C is independently hydrogen or $(C_1$-$C_6)$alkyl;

each occurrence of R_D is independently halogen, hydroxy, O$(C_1$-$C_4)$alkyl, C(=O)$(C_1$-$C_4)$alkyl, C(=O)O$(C_1$-$C_4)$alkyl;

each occurrence of R_F and $R_{F'}$ is independently hydrogen, $(C_1$-$C_6)$alkyl, phenyl, benzyl, or R_F and $R_{F'}$, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of

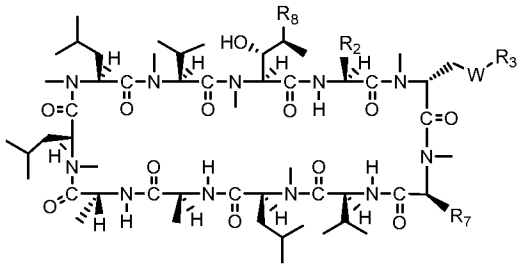
nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

p is an integer of 0, 1, 2, 3, 4, 5, or 6;

m is an integer of 1, 2, 3, 4, 5, or 6; and

n is an integer of 1, 2, 3, 4, 5 or 6.

[0022] In yet another aspect, a compound of Formula (I) is described:



(I)

or pharmaceutically acceptable salt thereof, wherein:

R_8 is n-butyl, (*E*)-but-2-enyl,  , $-(CH_2)_4-SR_9$, $-(CH_2)_4-(C=O)OR_9$, or $-(CH_2)_3-(C=O)OR_9$;

each occurrence of R_9 is independently hydrogen or (C_1-C_6)alkyl;

R_2 is ethyl, 1-hydroxyethyl, isopropyl or n-propyl;

W is O, CH_2, NR_1, or S;

R_1 is hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1-C_6)$alkyl, $-C(=O)O(C_1-C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

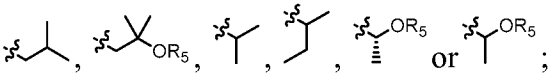
or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of (C_1-C_6)alkyl, phenyl and benzyl;

R_3 is:

(C_7-C_{12})alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

(C_7-C_{12})alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino; or

(C_7-C_{12})alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

R_7 is  ;

R_5 is:

H;

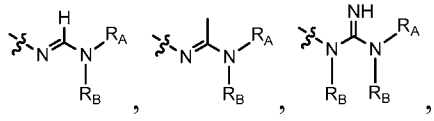
(C_1-C_6)alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

(C_2-C_6)alkenyl, optionally substituted by one or more groups which may be the same or different selected from hydroxy, (C_1-C_6)alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

(C_2-C_6)alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, $(C_3$-$C_7)$cycloalkyl, aryl, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -$O(C_1$-$C_6)$alkyl, -$C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

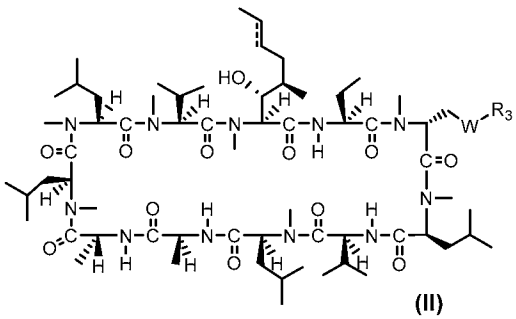
each occurrence of R_C is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

p is an integer of 0, 1, 2, 3, 4, or 5; and

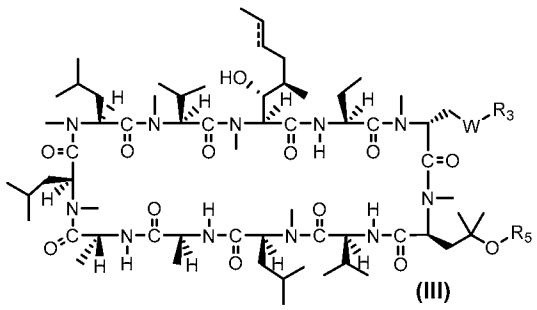
m is an integer of 1, 2, 3, 4 or 5.

[0023] In some embodiments, R_8 is n-butyl. In some embodiments, R_8 is (*E*)-but-2-enyl. In some embodiments, R_2 is ethyl.

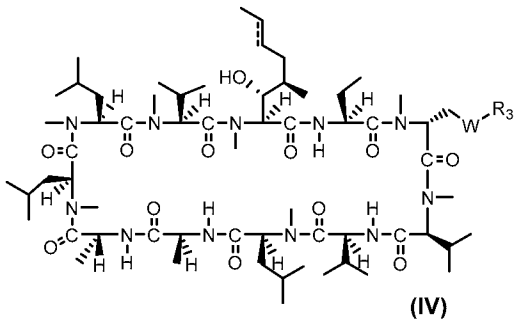
[0024] In yet another aspect, a compound having the structure of Formulae (II) through (V) is described:



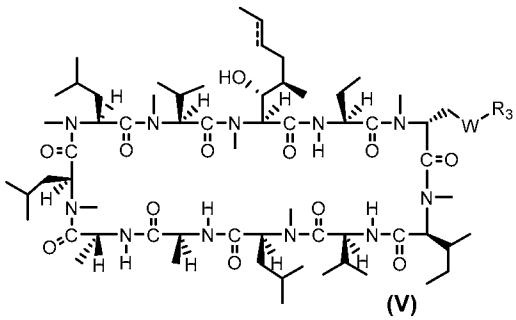
(II)



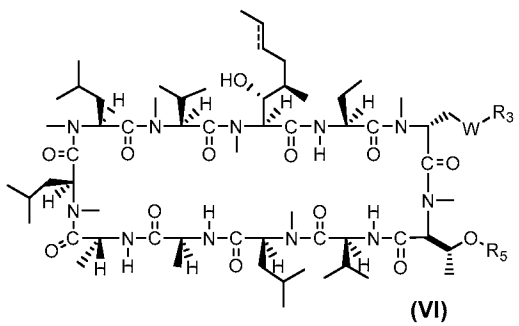
(III)



(IV)



(V)



(VI)

,

or pharmaceutically acceptable salt thereof, wherein:

represents a single bond or double bond;

each W is independently O, S, CH_2, or NR_1;

each R_1 is independently hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O$(C_1$-$C_6)$alkyl, -C(=O)O$(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of $(C_1$-$C_6)$alkyl, phenyl and benzyl;

each R_3 is independently:

$(C_7$-$C_{12})$alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

$(C_7$-$C_{12})$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$,

$(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$; or

$(C_7$-$C_{12})$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

each R_5 is independently:

H;

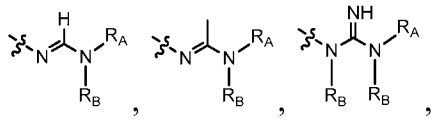
$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2$-$C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, aryl, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$, 

$NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, $(C_3$-$C_7)$cycloalkyl, aryl, $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

or R_A and R_B, together with the nitrogen atom to which they are attached, form -N=CH-$NR_FR_{F'}$, -N=CMe-$NR_FR_{F'}$, or -$NR_FC(=NH)NR_FR_{F'}$;

each occurrence of R_C is independently hydrogen or $(C_1$-$C_6)$alkyl;

each occurrence of R_D is independently halogen, hydroxy, $O(C_1$-$C_4)$alkyl, $C(=O)(C_1$-$C_4)$alkyl, $C(=O)O(C_1$-$C_4)$alkyl;

each occurrence of R_F and $R_{F'}$ is independently hydrogen, $(C_1$-$C_6)$alkyl, phenyl, benzyl, or R_F and $R_{F'}$, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

p is an integer of 0, 1, 2, 3, 4, 5, or 6;

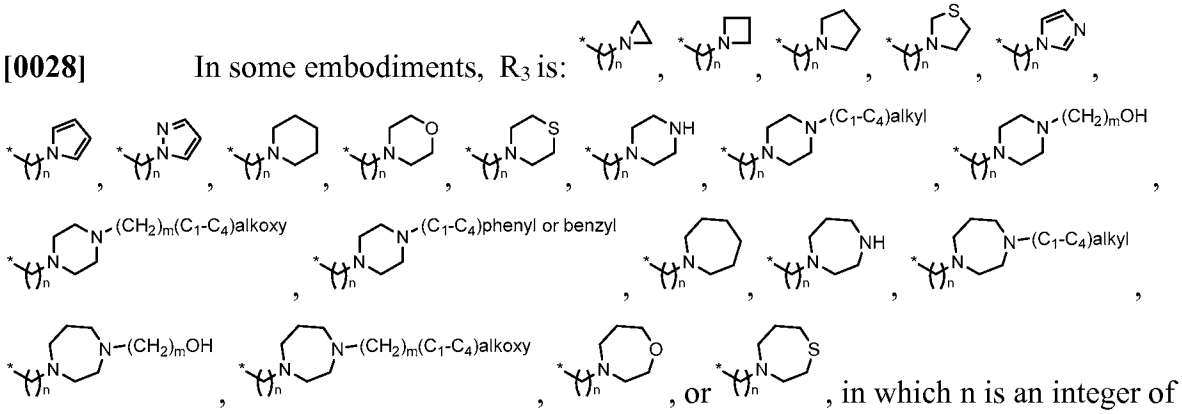
m is an integer of 1, 2, 3, 4, 5, or 6; and

n is an integer of 1, 2, 3, 4, 5 or 6.

[0025] In some embodiments, W is O. In some embodiments, W is S. In some embodiments, W is NR_1. In some embodiments, W is NH. In some embodiments, W is $N(C_1$-$C_4)$alkyl.

[0026] In some embodiments, R_3 is -$(CH_2)_nNR_AR_B$, wherein n is an integer of 7, 8, 9, 10, 11 or 12; and wherein each occurrence of R_A and R_B is independently hydrogen; $(C_1$-$C_4)$alkyl, optionally substituted by one or more groups R_D which may be the same or different, in which each occurrence of R_D is independently halogen, hydroxy, $O(C_1$-$C_4)$alkyl, $C(=O)(C_1$-$C_4)$alkyl, $C(=O)O(C_1$-$C_4)$alkyl; or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from $(C_1$-$C_4)$alkyl, phenyl and benzyl.

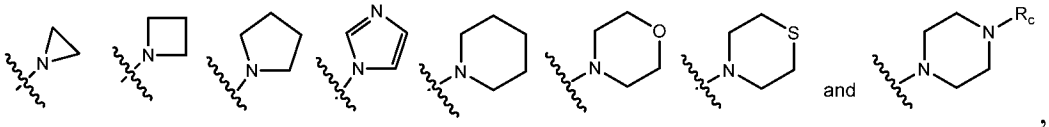
[0027] In some embodiments, R_3 is $-(CH_2)_nNR_AR_B$, wherein n is an integer of 7, 8, 9, 10, 11 or 12; and wherein R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from $(C_1\text{-}C_4)$alkyl, phenyl and benzyl.

[0028] In some embodiments, R_3 is: 

, in which n is an integer of 7, 8, 9, 10, 11 or 12, and m is an integer of 2, 3, or 4.

[0029] In some embodiments, R_5 is H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1\text{-}C_6)$alky, CH_2-O-$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)OR_A$, $(C_1\text{-}C_6)$-monoalkyl amine, $(C_1\text{-}C_6)$-dialkyl amine, or $(C_1\text{-}C_6)$-cyclic amine, in which said phenyl or benzyl is optionally substituted by one to three substitutents selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, and halogen; and R_A is H, $(C_1\text{-}C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1\text{-}C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1\text{-}C_6)$alkylO$(C_1\text{-}C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1\text{-}C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1\text{-}C_4)$alkyl; p is an integer of 0, 1, 2, 3, 4, or 5; and m is an integer of 1, 2, 3, 4 or 5.

[0030] In some embodiments, each occurrence R_A and R_B is independently H, $(C_1\text{-}C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1\text{-}C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, or $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1\text{-}C_6)$alkylO$(C_1\text{-}C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1\text{-}C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1\text{-}C_4)$alkyl.

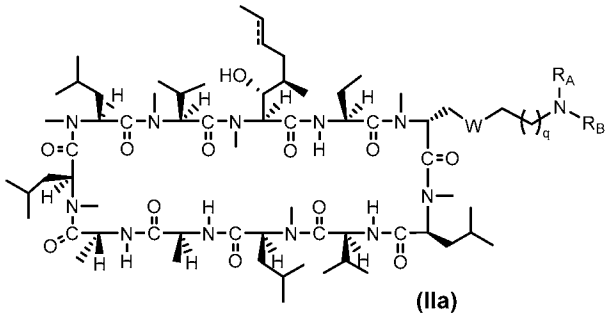
[0031] In some embodiments, R_A and R_B, together with the nitrogen atom to which they are attached, form a heterocycle selected from 

, in

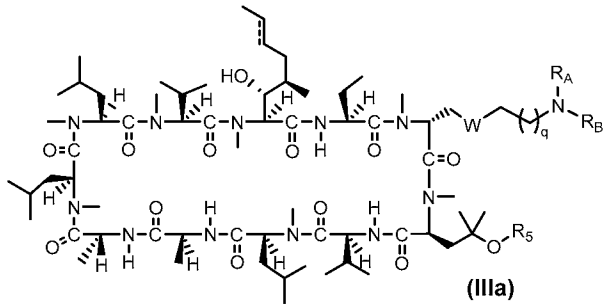
which R_C is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph, CH_2CH_2OH, or $CH_2CH_2O(C_1\text{-}C_4)$alkyl.

[0032] In some embodiments, ⁞ represents a single bond. In some embodiments, ⁞ represents a double bond.

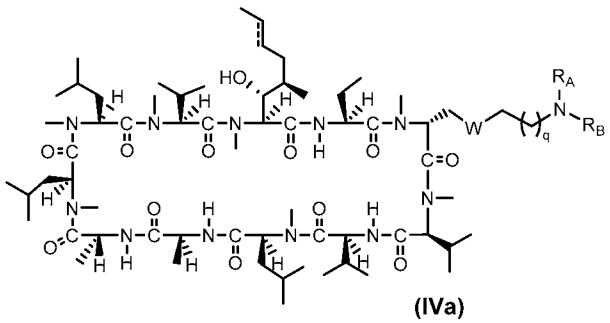
[0033] In yet another aspect, a compound having structure of Formulae (IIa)-(VIa) is described:



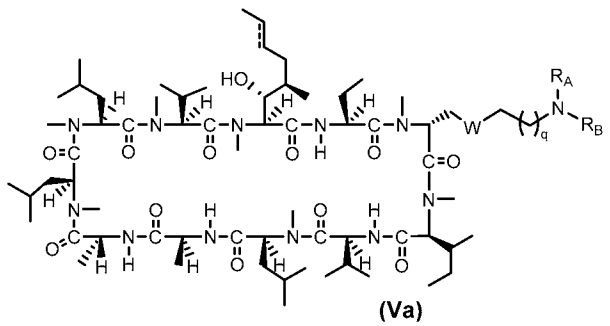
(IIa)



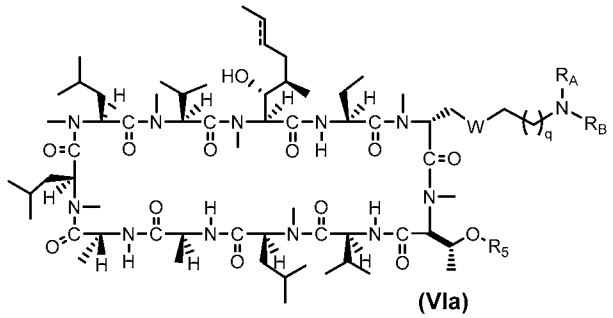
(IIIa)



(IVa)



(Va)



(VIa)

or a pharmaceutically acceptable salt thereof, wherein:

represents a single bond or double bond;

each W is independently O, S, or NR_1;

each R_1 is independently hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

each R_5 is independently:

H;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2\text{-}C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$,

$(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1$-$C_6)$alkyl;

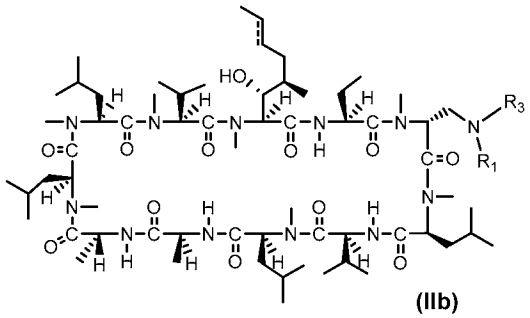
each occurrence of R_D is independently halogen, hydroxy, $O(C_1$-$C_4)$alkyl, $C(=O)(C_1$-$C_4)$alkyl, $C(=O)O(C_1$-$C_4)$alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5;

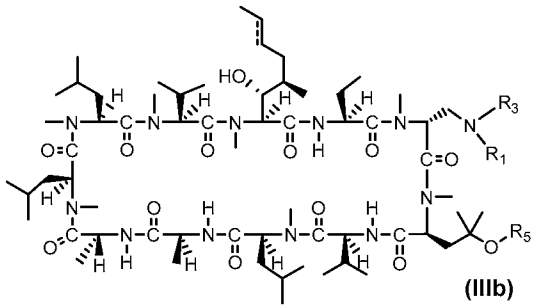
each of m and n is independently an integer of 1, 2, 3, 4 or 5; and

q is independently an integer of 7, 8, 9, 10, 11 or 12.

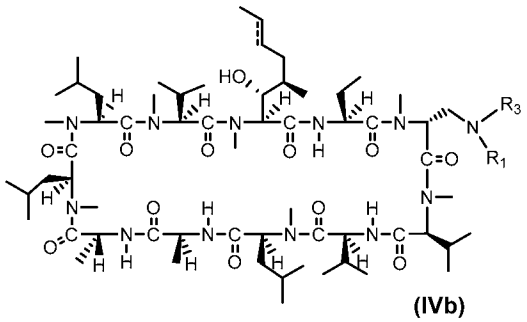
[0034] In yet another aspect, a compound having structure of Formulae (IIb)-(VIb) is described:



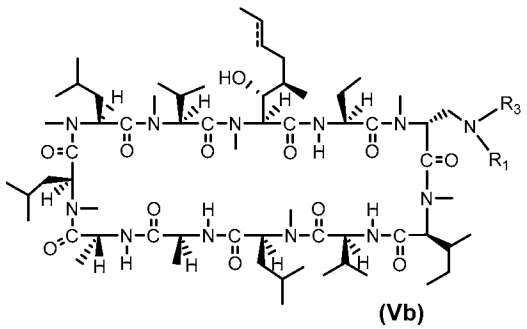
(IIb)



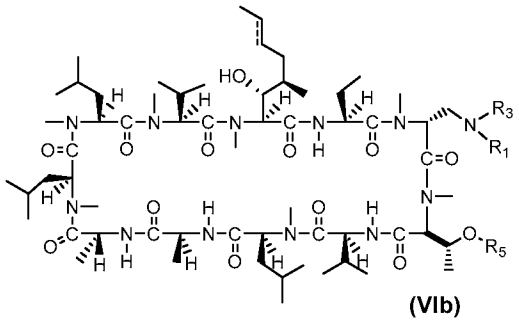
(IIIb)



(IVb)



(Vb)



(VIb)

or a pharmaceutically acceptable salt thereof, wherein:

represents a single bond or double bond;

each R_1 is independently hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of $(C_1$-$C_6)$alkyl, phenyl and benzyl;

each R_3 is independently:

$(C_7$-$C_{12})$alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

$(C_7$-$C_{12})$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$; or

$(C_7$-$C_{12})$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

each R_5 is independently:

H;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

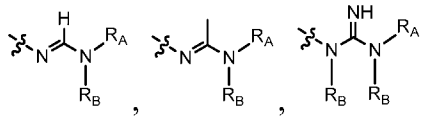
$(C_2$-$C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$,

$(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, aryl, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O(C_1-C_6)alkyl, -C(=O)O(C_1-C_6)alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or (C_1-C_6)alkyl;

each occurrence of R_D is independently halogen, hydroxy, O(C_1-C_4)alkyl, C(=O)(C_1-C_4)alkyl, C(=O)O(C_1-C_4)alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5; and

each of m, n and q is independently an integer of 1, 2, 3, 4 or 5.

[0035] In some embodiments, R_1 is hydrogen or (C_1-C_6)alkyl, and R_3 is (C_7-C_{12})alkyl.

[0036] In some embodiments, ⁞ represents a single bond or double bond;

each W is independently O, S, or NR_1;

each R_1 is independently hydrogen;

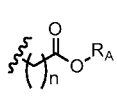
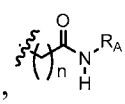
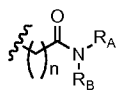
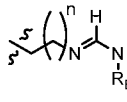
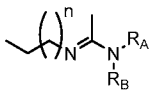
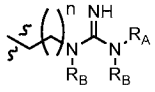
(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

each R_3 is independently  ,  ,  ,  ,  , or  ;

R_5 is:

H;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2\text{-}C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2\text{-}C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3\text{-}C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1\text{-}C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1$-$C_6)$alkyl;

each occurrence of R_D is independently halogen, hydroxy, $O(C_1$-$C_4)$alkyl, $C(=O)(C_1$-$C_4)$alkyl, $C(=O)O(C_1$-$C_4)$alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5; and

each of m and q is independently an integer of 1, 2, 3, 4 or 5; and

n is independently an integer of 6, 7, 8, 9, 10, 11 or 12.

[0037] In some embodiments, q is 1 or 2.

[0038] In some embodiments, W is O.

[0039] In some embodiments, W is S.

[0040] In some embodiments, W is NH.

[0041] In some embodiments, W is N-$(C_1$-$C_4)$alkyl.

[0042] In some embodiments, R_5 is H, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1$-$C_6)$alkyl, CH_2-O-$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)OR_A$, $(C_1$-$C_6)$-monoalkyl amine, $(C_1$-$C_6)$-dialkyl amine, or $(C_1$-$C_6)$-cyclic amine, in which said phenyl or benzyl is optionally substituted by one to three substitutents selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, and halogen; and R_A is H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkylO$(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl; p is an integer of 0, 1, 2, 3, 4, or 5; and m is an integer of 1, 2, 3, 4 or 5.

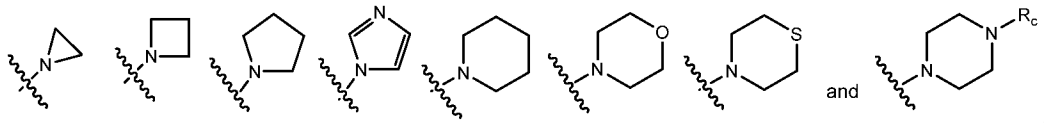
[0043] In some embodiments, R_5 is H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1$-$C_4)$alkyl, CH_2-O-$(C_1$-$C_4)$alkyl, $(CH_2)_2OH$, or $(CH_2)_2O(C_1$-$C_4)$alkyl.

[0044] In some embodiments, R_5 is H. In some embodiments, R_5 is methyl.

[0045] In some embodiments, each occurrence R_A and R_B is independently H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkyl-OH, $(CH_2)_pO(CH_2)_mOH$, or $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkyl-O-$(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl.

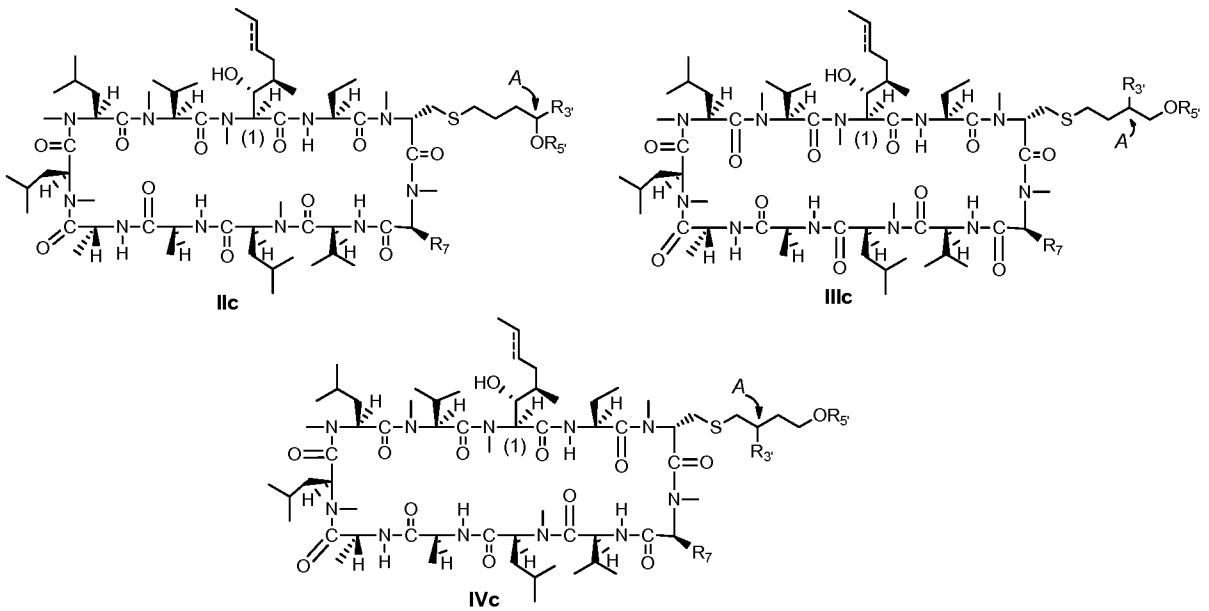
[0046] In some embodiments, occurrence R_A and R_B is independently H or (C_1-C_6)alkyl.

[0047] In some embodiments, R_A and R_B, together with the nitrogen atom to which they are attached, form a heterocycle selected from



, in which R_C is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph, CH_2CH_2OH, or $CH_2CH_2O(C_1$-$C_4)$alkyl.

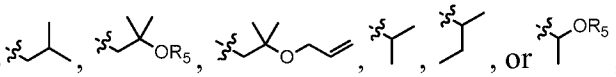
[0048] In another aspect, the present invention provides a compound of Formulae (IIc)-(IVc):

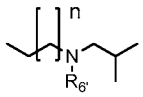


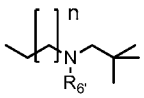
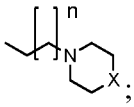
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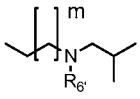
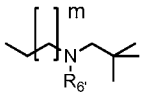
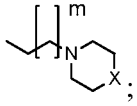
wherein

represents a single bond or double bond;

R_7 is  ;

$R_{3'}$ is Pr, i-Pr, $-CH_2(CH_2)_nNMe_2$, $-CH_2(CH_2)_nNEt_2$, $-CH_2(CH_2)_nOR_{5'}$,  ,

 , or  ;

R_5 and $R_{5'}$ are each independently H, Me, Et, Pr, *i*-Pr, $-CH_2(CH_2)_nNMe_2$, $-CH_2(CH_2)_nNEt_2$,  ,  , or  ;

$R_{6'}$ is H, Me, Et, Pr, i-Pr, i-Bu, or  ;

X is O, S, or $NR_{6'}$;

m is an integer of 1, 2, 3, 4, 5, or 6; and

n is an integer of 2, 3, 4, 5, or 6.

[0049] In some embodiments, the chiral centers *A* in the compound independently has a R or S configuration.

[0050] In yet another aspect, the present invention provides a pharmaceutical composition comprising at least one compound as described herein and a pharmaceutically-acceptable carrier.

[0051] In a further aspect, the present invention provides a method for treating or preventing a viral infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein.

[0052] In another aspect, the present invention provides a method for treating or preventing hepatitis C virus infection or hepatitis B virus in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein.

[0053] In another aspect, the present invention provides a method for treating or preventing HIV infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein.

[0054] In yet another aspect, the present invention provides a method for inhibiting a cyclophilin in a subject in need thereof, which comprises administrating to said subject an effective cyclophilin-inhibiting amount of at least one compound as described herein.

[0055] In yet another aspect, the present invention provides a method for treating or preventing diseases that are mediated by cyclophilins in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein.

[0056] In yet another aspect, the present invention provides a method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the disease is selected from inflammation, respiratory inflammation, rheumatoid arthritis, and dry eye.

[0057] In yet another aspect, the present invention provides a method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the disease is selected from neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's Diseases, and ALS; traumatic brain injury; stroke; and ischemia-reperfusion injury in the brain, heart, and kidney.

[0058] In yet another aspect, the present invention provides a method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the disease is selected from cardiovascular diseases, vascular stenosis, atherosclerosis, abdominal aortic aneurysms, cardiac hypertrophy, aortic rupture, pulmonary arterial hypertension, myocarditis and myocardial fibrosis, and ischaemic heart diseases.

[0059] In yet another aspect, the present invention provides a method for treating or preventing diseases or conditions in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the disease or condition is selected from cancer, obesity, diabetes, muscular dystrophy, and hair loss.

[0060] In yet another aspect, the present invention provides a method for treating or preventing diseases or conditions in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the diseases or conditions are selected from allergic conjunctivitis, atopic and vernal keratoconjunctivitis, atopic

keratoconjunctivitis, anterior uveitis, Behcet's disease, blepharitis, chronic ocular surface inflammation caused by viral infection, corneal transplant rejection, corneal sensitivity impaired due to surgery on the cornea or other surface of the eye, meibomian gland disease, ptyregia, ocular symptoms of graft versus host disease, ocular allergy, ocular cicatricial pemphigoid, Steven Johnson syndrome, vernal keratoconjunctivitis, uveitis, herpes simplex keratitis, ocular rosacea, and Pinguecula.

Detailed Description of the Invention

Definitions

[0061] The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

[0062] The terms "alkyl" and "alk" refer to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms. Exemplary "alkyl" groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. The term "(C_1-C_4)alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, and isobutyl. The term "(C_1-C_6)alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 6 carbon atoms, such as n-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, 2,2-dimethylbutyl, in addition to those exemplified for "(C_1-C_4)alkyl." "Substituted alkyl" refers to an alkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl,

alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. In the aforementioned exemplary substitutents, groups such as alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, heterocycle and aryl can themselves be optionally substituted.

[0063] The term "alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplaries of such groups include ethenyl or allyl. The term "C_2-C_6 alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon double bond, such as ethylenyl, propenyl, 2-propenyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl, 2-methy(*E*)-but-2-enyl, 2-methy(*Z*)-but-2-enyl, 2,3-dimethy-but-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-hex-1-enyl, (*E*)-pent-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-1-enyl, (*E*)-hex-1-enyl, , (*Z*)-hex-3-enyl, (*E*)-hex-3-enyl, and (*E*)-hex-1,3-dienyl. "Substituted alkenyl" refers to an alkenyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted.

[0064] The term "alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. An exemplary of such groups includes ethynyl. The term "C_2-C_6 alkynyl" refers to a straight

or branched chain hydrocarbon radical containing from 2 to 6 carbon atoms and at least one carbon-carbon triple bond, such as ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, pent-1-ynyl, pent-2-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl. "Substituted alkynyl" refers to an alkynyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted.

[0065] The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring. "C_3-C_7 cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl. "Substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together

with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cylic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substitutents can themselves be optionally substituted.

[0066] The term "cycloalkenyl" refers to a partially unsaturated cyclic hydrocarbon group containing 1 to 4 rings and 3 to 8 carbons per ring. Exemplaries of such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, *etc.* "Substituted cycloalkenyl" refers to a cycloalkenyl group substituted with one more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cylic substituents, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0067] The term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or

naphthyl. Where containing two or more aromatic rings (bicyclic, *etc.*), the aromatic rings of the aryl group may be joined at a single point (*e.g.*, biphenyl), or fused (*e.g.*, naphthyl, phenanthrenyl and the like). "Substituted aryl" refers to an aryl group substituted by one or more substituents, preferably 1 to 3 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include fused cylic groups, especially fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0068] The terms "heterocycle" and "heterocyclic" refer to fully saturated, or partially or fully unsaturated, including aromatic (*i.e.*, "heteroaryl") cyclic groups (for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 8 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term "heteroarylium" refers to a heteroaryl group bearing a quaternary nitrogen atom and thus a positive charge.) The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary monocyclic heterocyclic groups include azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl,

imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, hexahydrodiazepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, benzo[d][1,3]dioxolyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0069] "Substituted heterocycle" and "substituted heterocyclic" (such as "substituted heteroaryl") refer to heterocycle or heterocyclic groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen (*e.g.*, a single halogen substituent or multiple halo substitutents forming, in the latter case, groups such as CF_3 or an alkyl group bearing Cl_3), cyano, nitro, oxo (*i.e.*, =O), CF_3, OCF_3, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, aryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_e$, $P(=O)_2OR_e$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_d$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_e$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein each occurrence of R_a is independently hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl; each occurrence of R_b, R_c and R_d is independently hydrogen, alkyl, cycloalkyl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and each occurrence of R_e is independently alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, heterocycle, or aryl. The exemplary substitutents can themselves be optionally substituted. Exemplary substituents also include spiro-attached or fused cylic

substituents at any available point or points of attachment, especially spiro-attached cycloalkyl, spiro-attached cycloalkenyl, spiro-attached heterocycle (excluding heteroaryl), fused cycloalkyl, fused cycloalkenyl, fused heterocycle, or fused aryl, where the aforementioned cycloalkyl, cycloalkenyl, heterocycle and aryl substituents can themselves be optionally substituted.

[0070] The term "alkylamino" refers to a group having the structure -NHR', wherein R' is hydrogen, alkyl or substituted alkyl, cycloalkyl or substituted cyclolakyl, as defined herein. Examples of alkylamino groups include, but are not limited to, methylamino, ethylamino, n-propylamino, iso-propylamino, cyclopropylamino, n-butylamino, tert-butylamino, neopentylamino, n-pentylamino, hexylamino, cyclohexylamino, and the like.

[0071] The term "dialkylamino" refers to a group having the structure -NRR', wherein R and R' are each independently alkyl or substituted alkyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cyclolalkenyl, aryl or substituted aryl, heterocylyl or substituted heterocyclyl, as defined herein. R and R' may be the same or different in an dialkyamino moiety. Examples of dialkylamino groups include, but are not limited to, dimethylamino, methyl ethylamino, diethylamino, methylpropylamino, di(n-propyl)amino, di(iso-propyl)amino, di(cyclopropyl)amino, di(n-butyl)amino, di(tert-butyl)amino, di(neopentyl)amino, di(n-pentyl)amino, di(hexyl)amino, di(cyclohexyl)amino, and the like. In certain embodiments, R and R' are linked to form a cyclic structure. The resulting cyclic structure may be aromatic or non-aromatic. Examples of cyclic diaminoalkyl groups include, but are not limited to, aziridinyl, pyrrolidinyl, piperidinyl, morpholinyl, pyrrolyl, imidazolyl, 1,3,4-trianolyl, and tetrazolyl.

[0072] The terms "halogen" or "halo" refer to chlorine, bromine, fluorine or iodine.

[0073] Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

[0074] The compounds of the present invention may form salts which are also within the scope of this invention. Reference to a compound of the present invention is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of the present invention contains both a basic moiety, such as but not limited to a pyridine or imidazole, and an acidic moiety such as but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically

acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, *e.g.*, in isolation or purification steps which may be employed during preparation. Salts of a compound of the present invention may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0075] The compounds of the present invention which contain a basic moiety, such as but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (*e.g.*, 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates, naphthalenesulfonates (*e.g.*, 2-naphthalenesulfonates), nicotinates, nitrates, oxalates, pectinates, persulfates, phenylpropionates (*e.g.*, 3-phenylpropionates), phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates, tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

[0076] Compounds of the present invention which contain an acidic moiety, such but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl) ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.,* dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.,* decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.,* benzyl and phenethyl bromides), and others.

[0077] Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound that, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the present invention, or a salt and/or solvate thereof. Solvates of the compounds of the present invention include, for example, hydrates.

[0078] Compounds of the present invention, and salts or solvates thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

[0079] All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (*e.g.*, as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the International Union of Pure and Applied Chemistry (IUPAC) 1974 Recommendations. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

[0080] Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 90%, for example, equal to greater than 95%, equal to or greater than 99% pure ("substantially pure" compound I), which is then used or formulated as described herein. Such "substantially pure" compounds of the present invention are also contemplated herein as part of the present invention.

[0081] All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both *cis* (*Z*) and *trans* (*E*) alkene isomers, as well as *cis* and *trans* isomers of cyclic hydrocarbon or heterocyclic rings.

[0082] Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds.

[0083] Definitions of specific functional groups and chemical terms are described in more detail below. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, the entire contents of which are incorporated herein by reference.

[0084] Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0085] Isomeric mixtures containing any of a variety of isomer ratios may be utilized in accordance with the present invention. For example, where only two isomers are combined, mixtures containing 50:50, 60:40, 70:30, 80:20, 90:10, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0 isomer ratios are all contemplated by the present invention. Those of ordinary skill in the art will readily appreciate that analogous ratios are contemplated for more complex isomer mixtures.

[0086] The present invention also includes isotopically labeled compounds, which are identical to the compounds disclosed herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, or an enantiomer, diastereomer, tautomer, or pharmaceutically acceptable salt or solvate thereof, which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present

invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0087] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

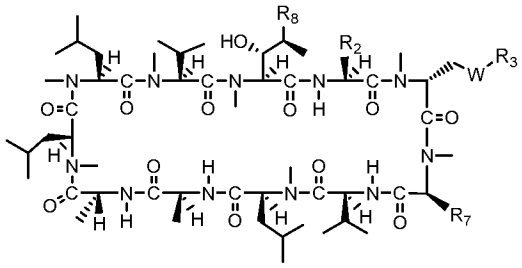
[0088] It will be appreciated that the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas of this invention, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Furthermore, this invention is not intended to be limited in any manner by the permissible substituents of

organic compounds. Combinations of substituents and variables envisioned by this invention are preferably those that result in the formation of stable compounds useful in the treatment, for example, of infectious diseases or proliferative disorders. The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

Compounds

[0089] The novel cyclosporin derivatives of the present invention are potent inhibitors of cyclophilins and are useful for inhibiting viruses such as HCV, HBV, and HIV.

[0090] In one aspect, the present invention provides a compound Formula (I):



(I)

or pharmaceutically acceptable salt thereof, wherein:

R_8 is n-butyl, (*E*)-but-2-enyl,  , $-(CH_2)_4-SR_9$, $-(CH_2)_4-(C=O)OR_9$, or $-(CH_2)_3-(C=O)OR_9$;

each occurrence of R_9 is independently hydrogen or (C_1-C_6)alkyl;

R_2 is ethyl, 1-hydroxyethyl, isopropyl or n-propyl;

W is O, S, CH_2, or NR_1;

R_1 is hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1-C_6)$alkyl, $-C(=O)O(C_1-C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of (C_1-C_6)alkyl, phenyl and benzyl;

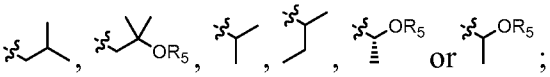
R_3 is:

H;

(C_7-C_{12})alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

(C_7-C_{12})alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino; or

(C_7-C_{12})alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

R_7 is  ;

R_5 is:

H;

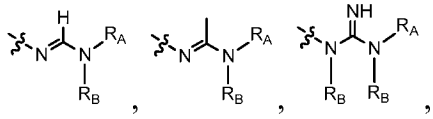
(C_1-C_6)alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

(C_2-C_6)alkenyl, optionally substituted by one or more groups which may be the same or different selected from hydroxy, (C_1-C_6)alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

(C_2-C_6)alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

(C_3-C_7)cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, aryl (e.g., phenyl), OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl (e.g., phenyl), $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O(C_1-C_6)alkyl, -C(=O)O(C_1-C_6)alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

p is an integer of 0, 1, 2, 3, 4, or 5; and

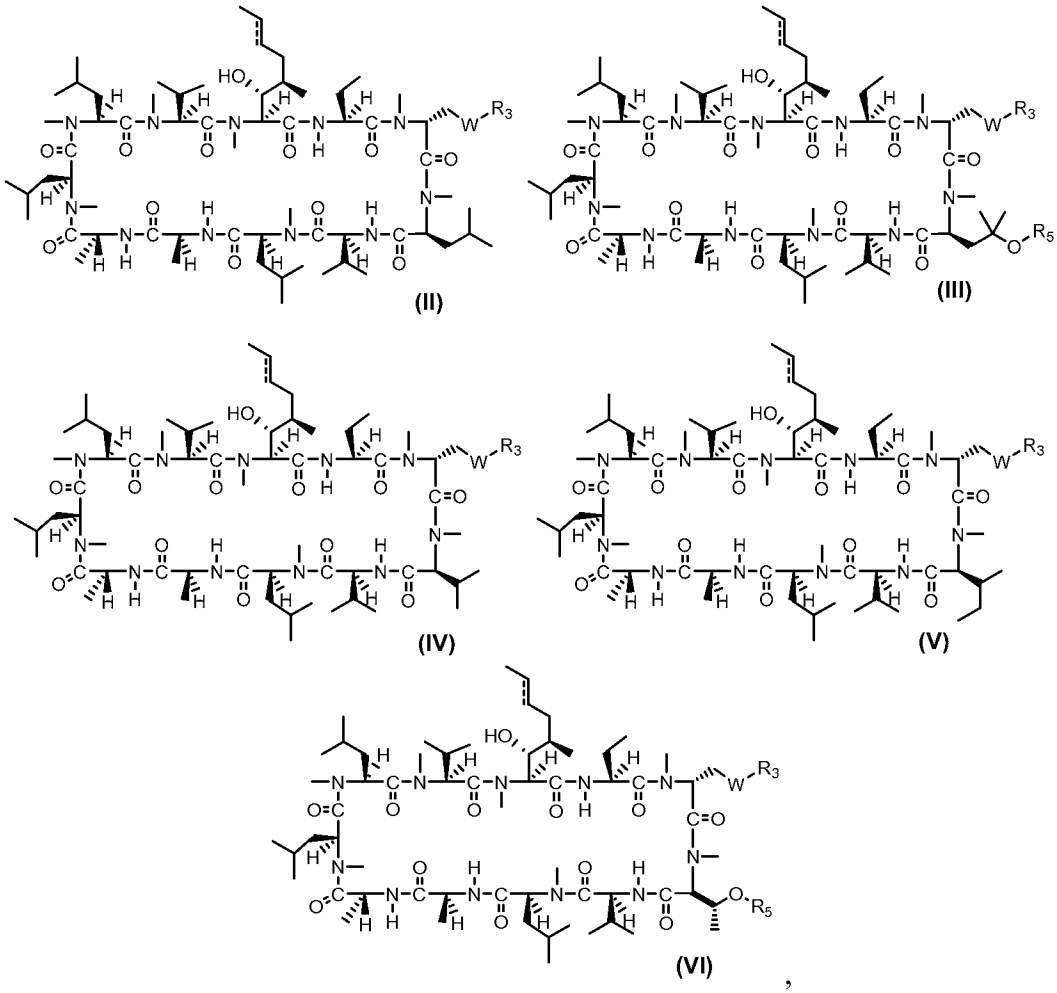
m is an integer of 1, 2, 3, 4 or 5.

[0091] In certain embodiments, R_3 is $(C_7\text{-}C_{10})$alkyl. In certain other embodiments, R_3 is $(C_7\text{-}C_8)$alkyl. In yet other embodiments, R_3 is $(C_7\text{-}C_{12})$ linear alkyl. In yet other embodiments, R_3 is $(C_7\text{-}C_{10})$ linear alkyl. In yet other embodiments, R_3 is $(C_7\text{-}C_8)$ linear alkyl. In yet other embodiments, R_3 is $(CH_2)_pS(CH_2)_nCH_3$, wherein p and n are each independently interger of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11, and wherein R3 may be further optionally substituted by one or more groups R_4 which may be the same or different as described herein.

[0092] In certain embodiments, R_4 is hydroxyl. In certain other embodiments, R_4 is $C(=O)OR_A$.

[0093] In certain embodiments, R_8 is n-butyl. In certain other embodiments, R_8 is (*E*)-but-2-enyl. In certain other embodiments, R_8 is  . In yet other embodiments, R_8 is $-(CH_2)_4\text{-}SR_9$. In yet other embodiments, R_8 is $-(CH_2)_4\text{-}(C=O)OR_9$. In yet other embodiments, R_8 is $-(CH_2)_3\text{-}(C=O)OR_9$. In certain embodiments, each occurrence of R_9 is independently hydrogen. In certain other embodiments, each occurrence of R_9 is independently $(C_1\text{-}C_6)$alkyl. In certain embodiments, R_2 is ethyl.

[0094] In certain embodiments, the compound of Formula I has the structure of Formulae (II) through (VI):



or pharmaceutically acceptable salt thereof, wherein:

┇ represents a single bond or double bond;

each W is independently O, S or NR_1;

each R_1 is independently hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of (C_1-C_6)alkyl, phenyl and benzyl;

each R_3 is independently:

H;

(C_7-C_{12})alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

(C_7-C_{12})alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$; or

(C_7-C_{12})alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

each R_5 is independently:

H;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

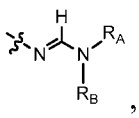
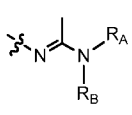
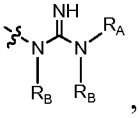
(C_2-C_6)alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, aryl (e.g., phenyl),

$(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, $(C_3$-$C_7)$cycloalkyl, aryl (e.g., phenyl), OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  ,  ,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl (e.g., phenyl), $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O(C_1-C_6)alkyl, -C(=O)O(C_1-C_6)alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

or R_A and R_B, together with the nitrogen atom to which they are attached, form -N=CH-$NR_FR_{F'}$, -N=CMe-$NR_FR_{F'}$, or -NR_FC(=NH)$NR_FR_{F'}$;

each occurrence of R_C is independently hydrogen or (C_1-C_6)alkyl;

each occurrence of R_D is independently halogen, hydroxy, O(C_1-C_4)alkyl, C(=O)(C_1-C_4)alkyl, C(=O)O(C_1-C_4)alkyl;

each occurrence of R_F and $R_{F'}$ is independently hydrogen, (C_1-C_6)alkyl, phenyl, benzyl, or R_F and $R_{F'}$, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

p is an integer of 0, 1, 2, 3, 4, 5, or 6;

m is an integer of 1, 2, 3, 4, 5, or 6; and

n is an integer of 1, 2, 3, 4, 5 or 6.

[0095] In certain embodiments, W is O. In certain other embodiments, W is S. In yet other embodiments, W is NH. In yet other embodiments, W is NR_1. In certain embodiments, W is N-(C_1-C_4)alkyl.

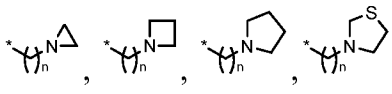
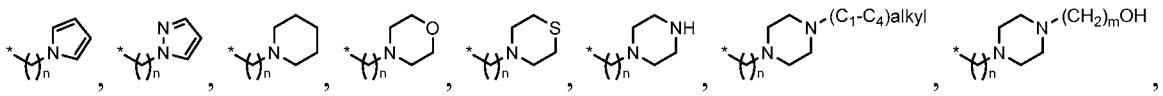
[0096] In certain embodiments, m is 1. In certain other embodiments, m is 2. In yet other embodiments, m is 3. In yet other embodiments, m is 4 or 5.

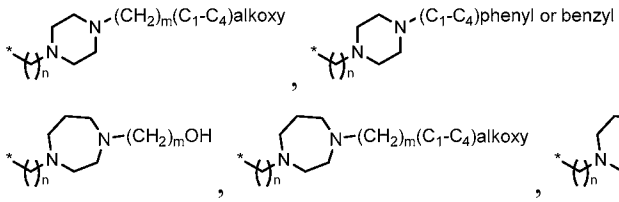
[0097] In certain embodiments, p is 0. In certain other embodiments, p is 1. In yet other embodiments, m is 2. In yet other embodiments, m is 3, 4 or 5.

[0098] In certain embodiments, R_3 is -$(CH_2)_nNR_AR_B$, wherein n is an integer of 7, 8, 9, 10, 11 or 12; and wherein each occurrence of R_A and R_B is independently hydrogen; (C_1-C_4)alkyl, optionally substituted by one or more groups R_D which may be the same or different, in which each occurrence of R_D is independently halogen, hydroxy, O(C_1-C_4)alkyl, C(=O)(C_1-C_4)alkyl, C(=O)O(C_1-C_4)alkyl; or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from (C_1-C_4)alkyl, phenyl and benzyl.

[0099] In certain embodiments, R_3 is -$(CH_2)_nNR_AR_B$, wherein n is an integer of 7, 8, 9, 10, 11 or 12; and wherein R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from (C_1-C_4)alkyl, phenyl and benzyl.

[0100] In certain embodiments, n is 7 or 8. In yet other embodiments, n is 9 or 10. In yet other embodiments, n is 11 or 12.

[0101] In certain embodiments, R_3 is  ,  ,

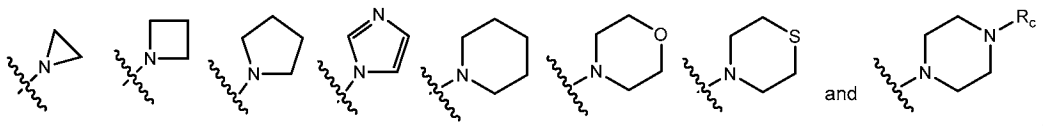


, in which n is an integer of 7, 8, 9, 10, 11 or 12, and m is an integer of 2, 3, or 4. In certain embodiments, n is 7 or 8. In yet other embodiments, n is 9 or 10. In yet other embodiments, n is 11 or 12. In certain embodiments, m is 2. In certain other embodiments, m is 3. In certain other embodiments, m is 4.

[0102] In certain embodiments, R_5 is H, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, phenyl, benzyl, $CH_2\text{-}S\text{-}(C_1\text{-}C_6)$alky, $CH_2\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)OR_A$, $(C_1\text{-}C_6)$-monoalkyl amine, $(C_1\text{-}C_6)$-dialkyl amine, or $(C_1\text{-}C_6)$-cyclic amine, in which said phenyl or benzyl is optionally substituted by one to three substitutents selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, and halogen; and R_A is H, $(C_1\text{-}C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1\text{-}C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1\text{-}C_6)$alkyl$O(C_1\text{-}C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1\text{-}C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1\text{-}C_4)$alkyl; p is an integer of 0, 1, 2, 3, 4, or 5; and m is an integer of 1, 2, 3, 4 or 5.

[0103] In certain embodiments, R_5 is H. In certain other embodiments, R_5 is methyl. In yet other embodiments, R_5 is $CH_2\text{-}S\text{-}(C_1\text{-}C_6)$alky, e.g., $CH_2\text{-}S\text{-}CH_3$. In yet other embodiments, R_5 is $CH_2\text{-}O\text{-}(C_1\text{-}C_6)$alkyl, e.g., $CH_2\text{-}O\text{-}CH_2\text{-}CH_3$. In yet other embodiments, R_5 is $(C_2\text{-}C_6)$alkenyl, e.g., $CH_2\text{-}CH{=}CH_2$. In yet other embodiments, R_5 is benzyl. In yet other embodiments, R_5 is $(C_2\text{-}C_6)$OH. In yet other embodiments, R_5 is $(C_1\text{-}C_6)$-monoalkyl amine, e.g., $CH_2\text{-}NH\text{-}Me$. In yet other embodiments, R_5 is $(C_1\text{-}C_6)$-dialkyl amine, e.g., $CH_2\text{-}CH_2\text{-}N(Et)_2$. In yet other embodiments, R_5 is $(C_1\text{-}C_6)$-cyclic amine, e.g., $CH_2\text{-}CH_2$-morpholine.

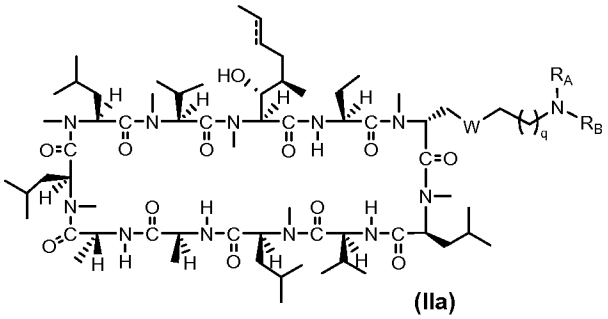
[0104] In certain embodiments, each occurrence R_A and R_B is independently H, $(C_1\text{-}C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1\text{-}C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, or $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1\text{-}C_6)$alkyl$O(C_1\text{-}C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1\text{-}C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1\text{-}C_4)$alkyl. In certain other embodiments, R_A and R_B, together with the nitrogen atom to which they are attached, form a heterocycle selected from



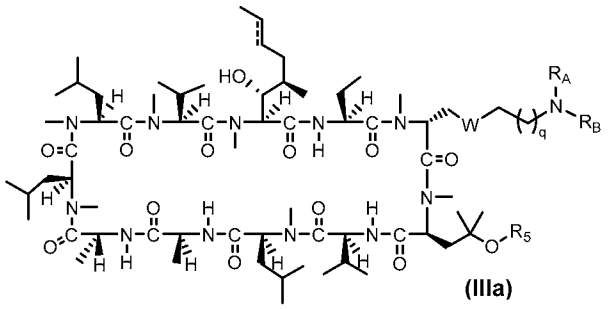
, in which R_C is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph, CH_2CH_2OH, or $CH_2CH_2O(C_1\text{-}C_4)$alkyl.

[0105] In certain embodiments, wherein ⁞ represents a single bond. In certain other embodiments, wherein ⁞ represents a double bond.

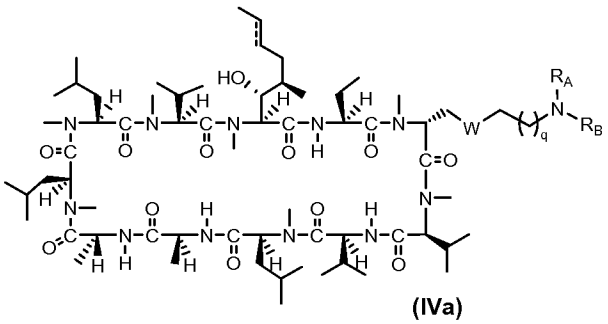
[0106] In another aspect, the present invention provides a compound of Formulae (IIa)-(VIa):



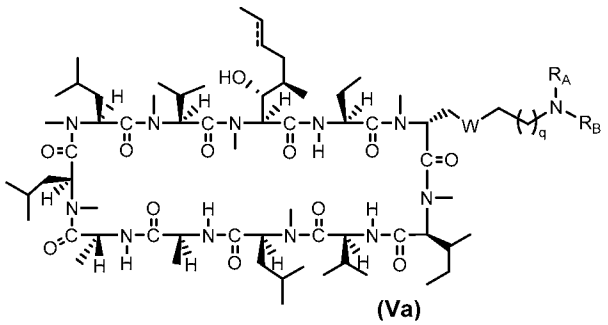
(IIa)



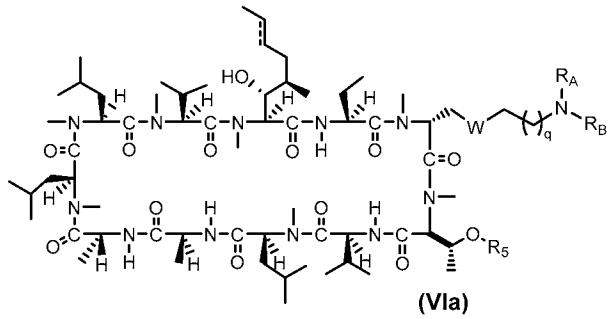
(IIIa)



(IVa)



(Va)



(VIa)

or a pharmaceutically acceptable salt thereof, wherein:

represents a single bond or double bond;

each W is independently O, S, or NR_1;

each R_1 is independently hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

each R_5 is independently:

H;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2\text{-}C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$,

$O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_6 is independently halogen, hydroxy, aryl (e.g., phenyl), $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1$-$C_6)$alkyl;

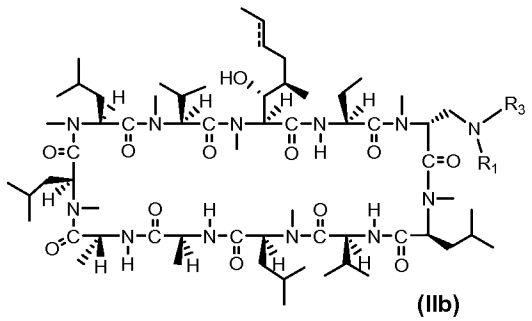
each occurrence of R_D is independently halogen, hydroxy, $O(C_1$-$C_4)$alkyl, $C(=O)(C_1$-$C_4)$alkyl, $C(=O)O(C_1$-$C_4)$alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5; and

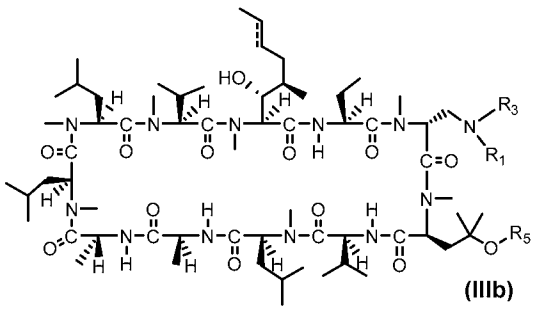
each of m and n is independently an integer of 1, 2, 3, 4 or 5; and

q is independently an integer of 6, 7, 8, 9, 10 or 11.

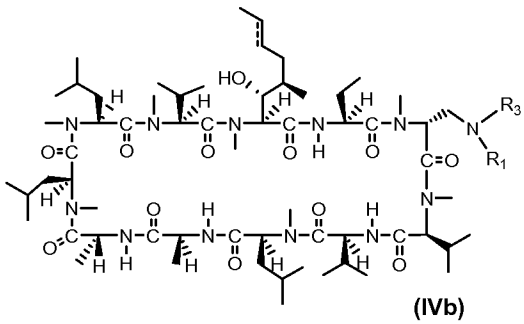
[0107] In another aspect, the present invention provides a compound of Formulae (IIb)-(VIb):



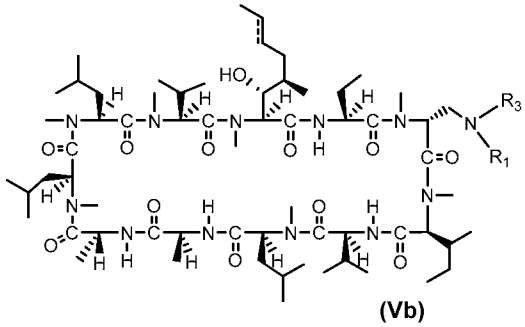
(IIb)



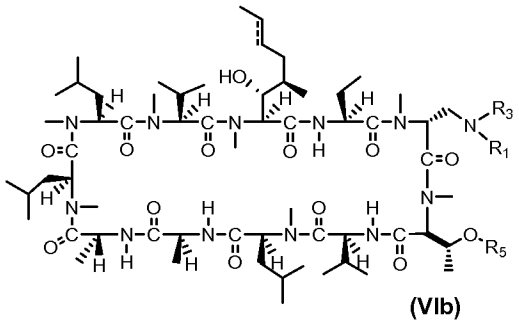
(IIIb)



(IVb)



(Vb)



(VIb)

or a pharmaceutically acceptable salt thereof, wherein:

⁞ represents a single bond or double bond;

each R_1 is independently hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of $(C_1\text{-}C_6)$alkyl, phenyl and benzyl;

each R_3 is independently:

H;

(C_7-C_{12})alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

(C_7-C_{12})alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$; or

(C_7-C_{12})alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

each R_5 is independently:

H;

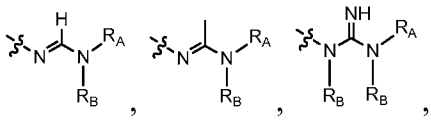
(C_1-C_6)alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

(C_2-C_6)alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

(C_2-C_6)alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

(C_3-C_7)cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, $(C_3$-$C_7)$cycloalkyl, aryl (e.g., phenyl), OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl (e.g., phenyl), $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group

consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

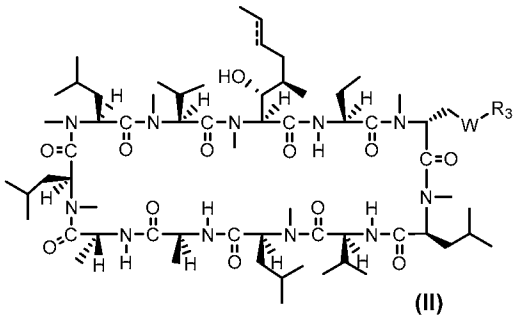
each occurrence of R_C is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

each occurrence of R_D is independently halogen, hydroxy, $O(C_1\text{-}C_4)$alkyl, $C(=O)(C_1\text{-}C_4)$alkyl, $C(=O)O(C_1\text{-}C_4)$alkyl;

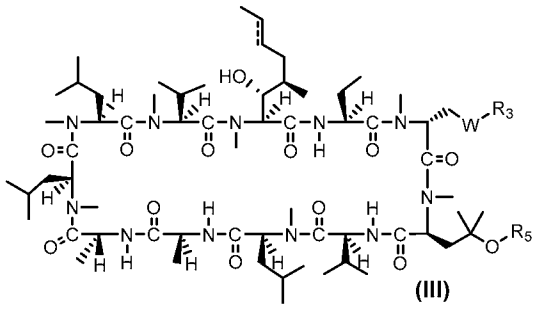
each p is independently an integer of 0, 1, 2, 3, 4, or 5; and

each of m, n and q is independently an integer of 1, 2, 3, 4 or 5.

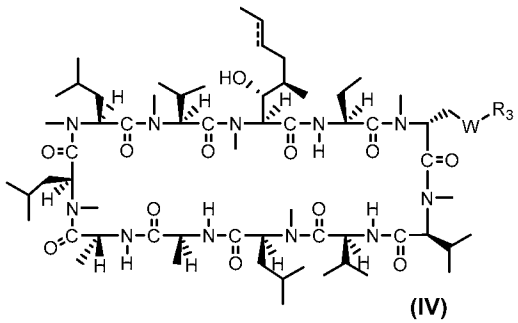
[0108] In certain embodiments, the compound of Formula I has the structure of Formulae (II) through (VI):



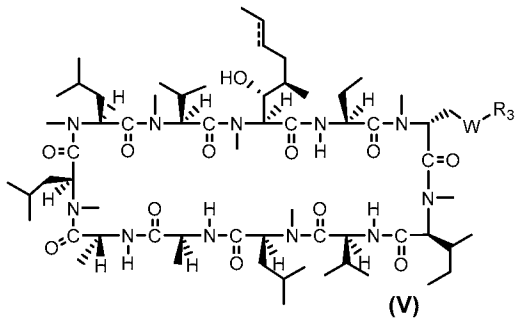
(II)



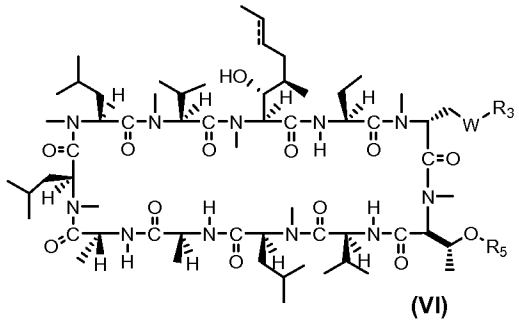
(III)



(IV)



(V)



(VI)

,

or a pharmaceutically acceptable salt thereof, wherein:

represents a single bond or double bond;

each W is independently O, S, or NR_1;

each R_1 is independently hydrogen;

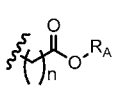
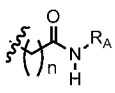
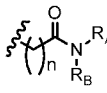
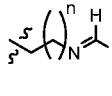
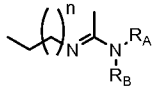
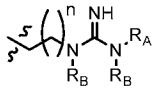
$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

each R_3 is independently  ,  ,  ,  ,  , or  ;

each R_5 is independently:

H;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2\text{-}C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, aryl (e.g., phenyl), $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_e(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

(C_2-C_6)alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

(C_3-C_7)cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_6 is independently halogen, hydroxy, aryl (e.g., phenyl), $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1$-$C_6)$alkyl;

each occurrence of R_D is independently halogen, hydroxy, $O(C_1$-$C_4)$alkyl, $C(=O)(C_1$-$C_4)$alkyl, $C(=O)O(C_1$-$C_4)$alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5; and

each of m and q is independently an integer of 1, 2, 3, 4 or 5; and

n is independently an integer of 6, 7, 8, 9, 10 or 11.

[0109] In certain embodiments, q is 1. In certain other embodiments, q is 2.

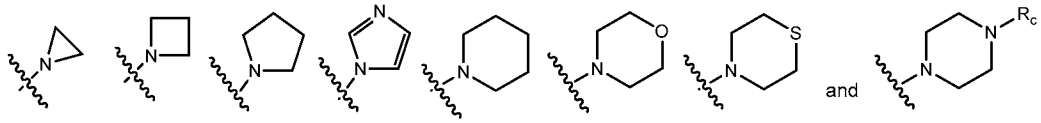
[0110] In certain embodiments, W is S. In certain other embodiments, W is O. In yet other embodiments, W is NH. In yet other embodiments, W is N-$(C_1$-$C_4)$alkyl.

[0111] In certain embodiments, R_1 is hydrogen. In certain other embodiments, R_1 is $(C_1$-$C_6)$alkyl. In certain embodiments, R_3 is $(C_7$-$C_{10})$alkyl. In certain other embodiments, R_3 is $(C_7$-$C_8)$alkyl. In yet other embodiments, R_3 is $(C_7$-$C_{12})$ linear alkyl. In yet other embodiments, R_3 is $(C_7$-$C_{10})$ linear alkyl. In yet other embodiments, R_3 is $(C_7$-$C_8)$ linear alkyl. In certain other embodiments, R_3 is $NR_CCH_2(CH_2)_pNR_AR_B$, wherein p is an integer of 6, 7, 8, 9, 10 or 11.

[0112] In certain embodiments, R_5 is H, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1$-$C_6)$alkyl, CH_2-O-$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)OR_A$, $(C_1$-$C_6)$-monoalkyl amine, $(C_1$-$C_6)$-dialkyl amine, or $(C_1$-$C_6)$-cyclic amine, in which said phenyl or benzyl is optionally substituted by one to three substitutents selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, and halogen; and R_A is H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkyl$O(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl; p is an integer of 0, 1, 2, 3, 4, or 5; and m is an integer of 1, 2, 3, 4 or 5.

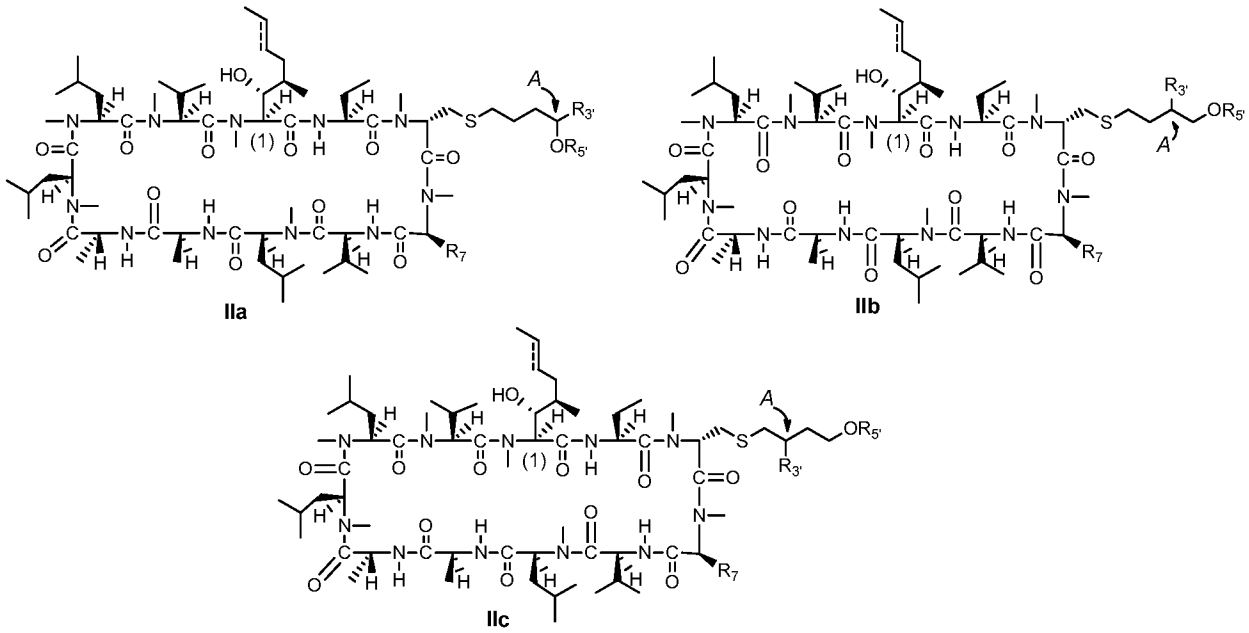
[0113] In certain other embodiments, R_5 is H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1$-$C_4)$alkyl, CH_2-O-$(C_1$-$C_4)$alkyl, $(CH_2)_2OH$, or $(CH_2)_2O(C_1$-$C_4)$alkyl. In certain embodiments, R_5 is H. In certain other embodiments, R_5 is methyl.

[0114] In certain embodiments, each occurrence R_A and R_B is independently H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, or $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkylO$(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl. In certain other embodiments, each occurrence R_A and R_B is independently H or $(C_1$-$C_6)$alkyl. In yet other embodiments, R_A and R_B, together with the nitrogen atom to which they are attached, form a heterocycle selected from



, in which R_C is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph, or CH_2CH_2OH and $CH_2CH_2OR_d$.

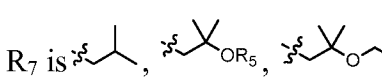
[0115] In certain embodiments, a compound having structure of Formulae (IIc)-(IVc) is described:

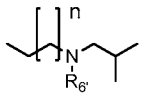


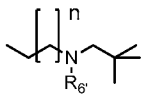
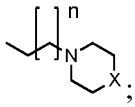
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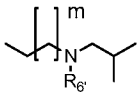
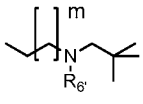
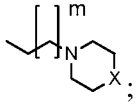
wherein

represents a single bond or double bond;

R_7 is  ;

$R_{3'}$ is Pr, i-Pr, $-CH_2(CH_2)_nNMe_2$, $-CH_2(CH_2)_nNEt_2$, $-CH_2(CH_2)_nOR_{5'}$,  ,

 , or  ;

R_5 and $R_{5'}$ are each independently H, Me, Et, Pr, *i*-Pr, $-CH_2(CH_2)_nNMe_2$, $-CH_2(CH_2)_nNEt_2$,  ,  , or  ;

$R_{6'}$ is H, Me, Et, Pr, i-Pr, i-Bu, or  ;

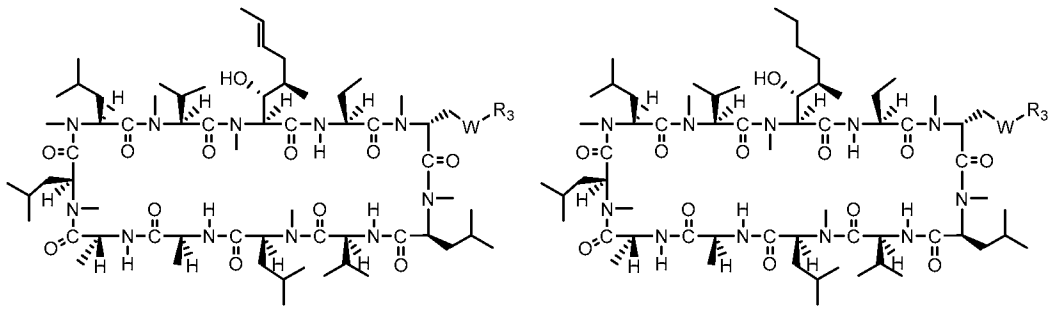
X is O, S, or $NR_{6'}$;

m is an integer of 1, 2, 3, 4, 5, or 6; and

n is an integer of 2, 3, 4, 5, or 6.

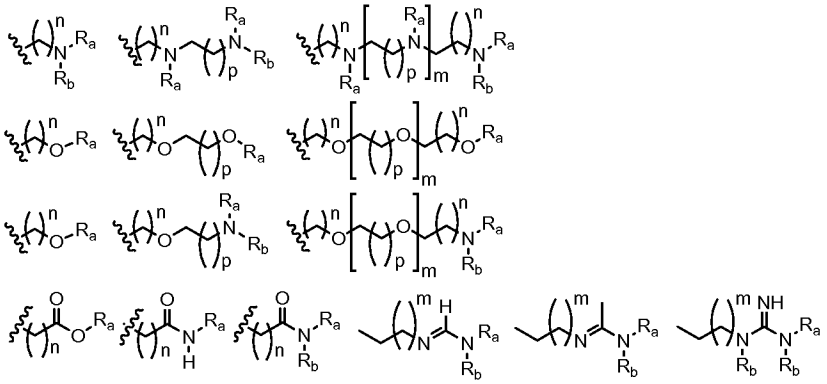
[0116] In certain embodiments, each of the chiral centers *A* in the compound independently has a R or S configuration.

[0117] In one aspect, the present invention provides a compound selected from the following:



W=O, S, N-H, and N-R_a

R_3 = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

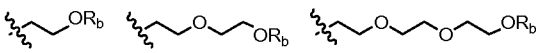


n = 7, 8, 9, 10, 11, 12

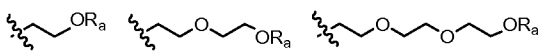
m = 1, 2, 3, 4, 5, 6

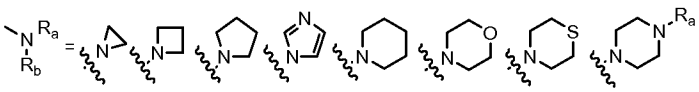
p = 1, 2, 3, 4, 5, 6

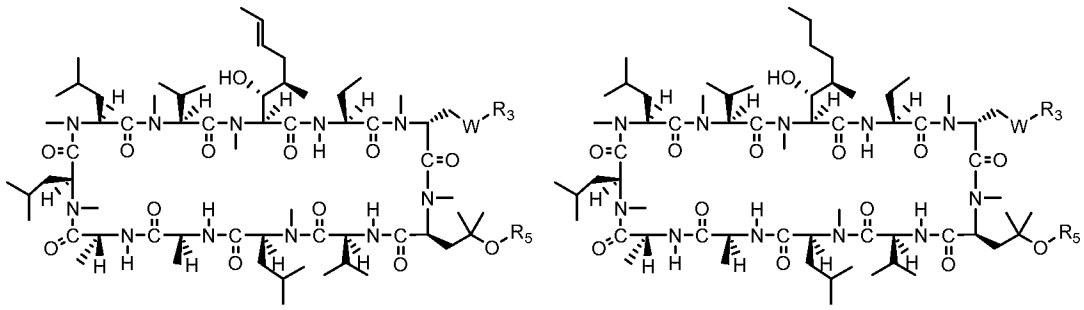
R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

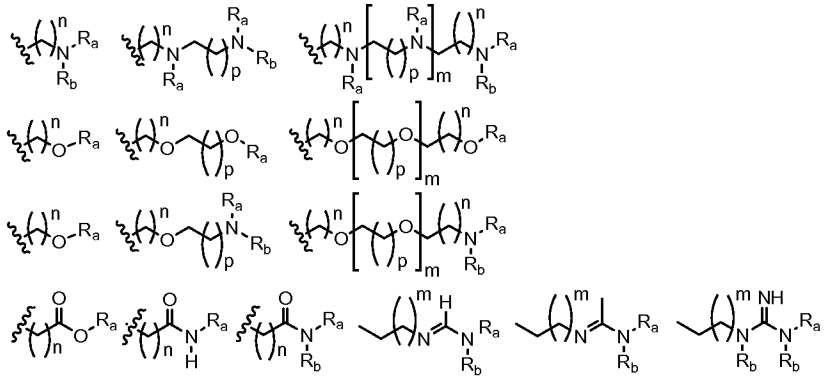






W=O, S, N-H, or N-R_a

R_3 = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

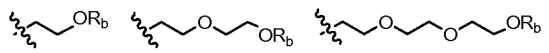


n = 7, 8, 9, 10, 11, 12

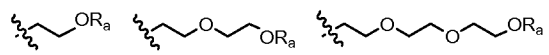
m = 1, 2, 3, 4, 5, 6

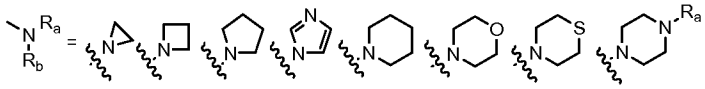
p = 1, 2, 3, 4, 5, 6

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

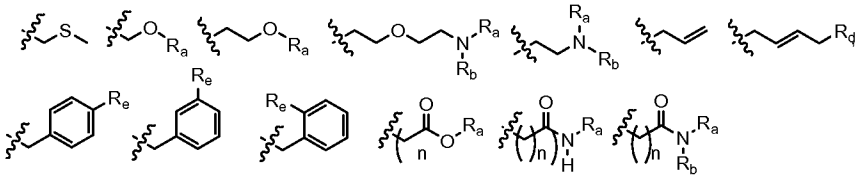


R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



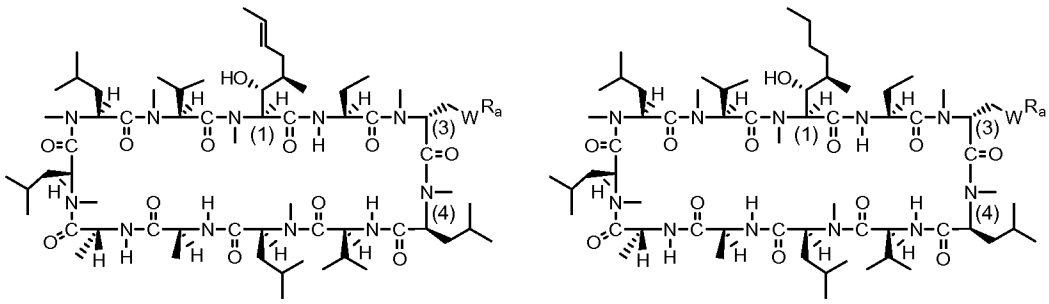


R_5 = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_d = R_a, OR_a, R_3

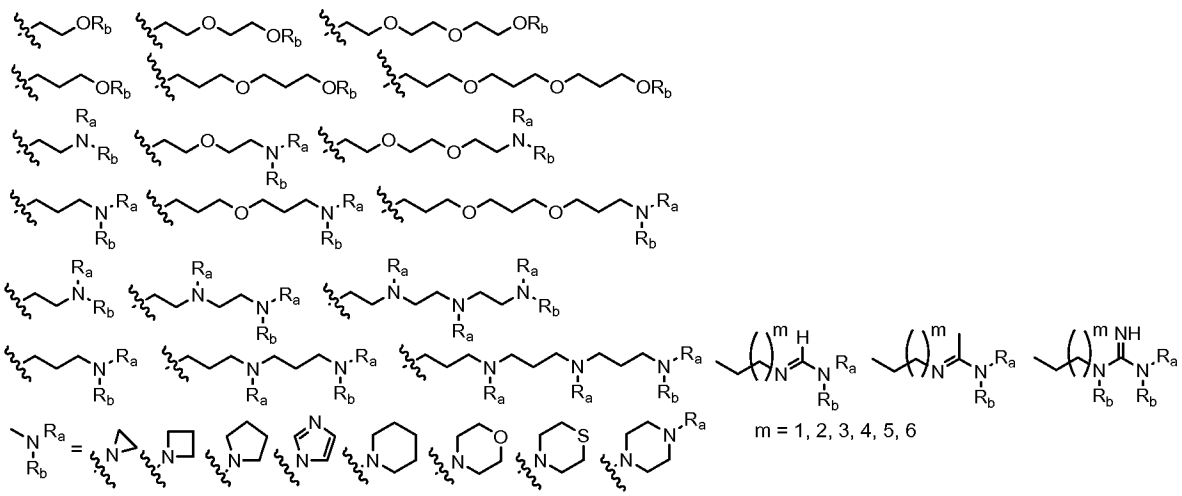
R_e = H, Me, Et, OR_a, R_3, CH_2OR_a, $CH_2CH_2OR_a$,



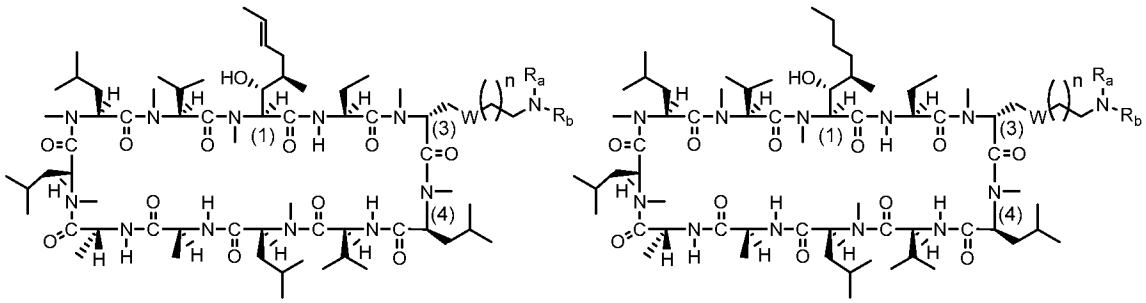
W=O, S, N-H, or N-R_a

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



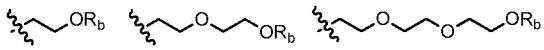
m = 1, 2, 3, 4, 5, 6



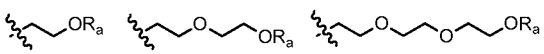
W=O, S, N-H, or N-R_a

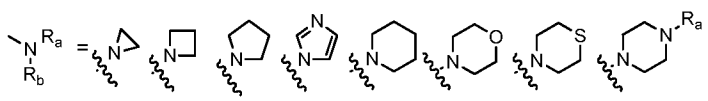
n = 6, 7, 8, 9, 10, or 11

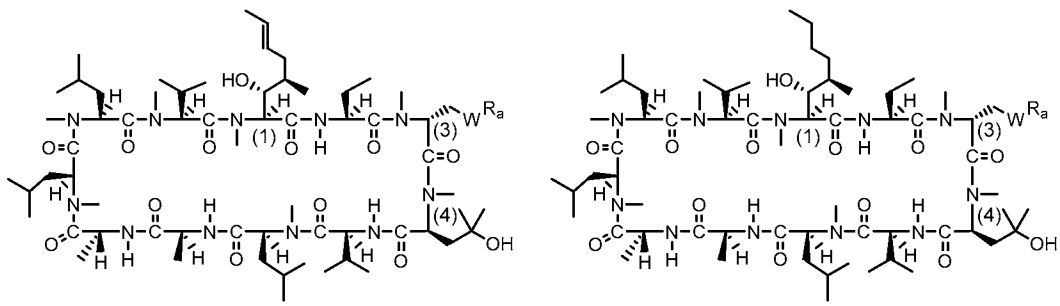
R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



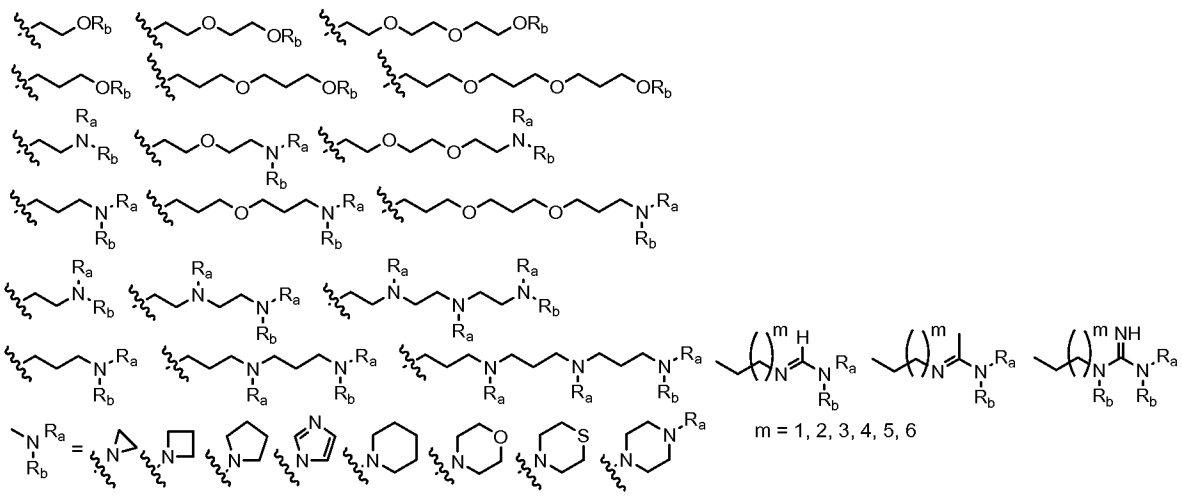




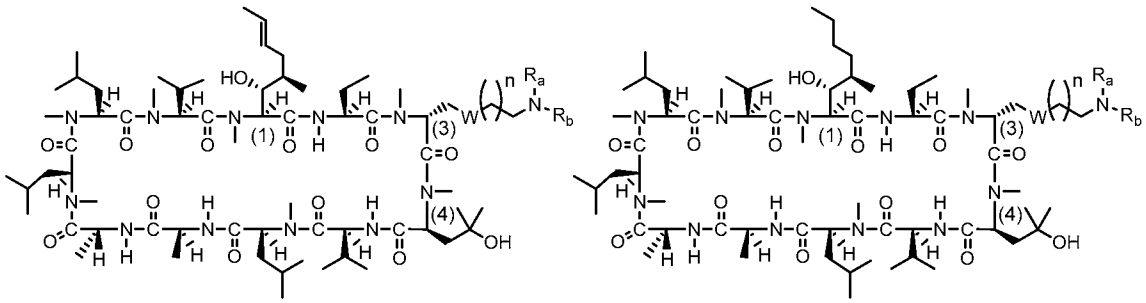
W=O, S, N-H, or N-R_a

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



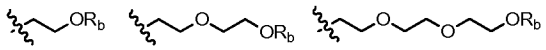
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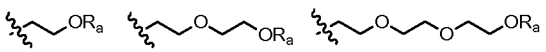
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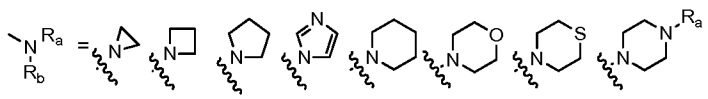
n = 6, 7, 8, 9, 10, or 11

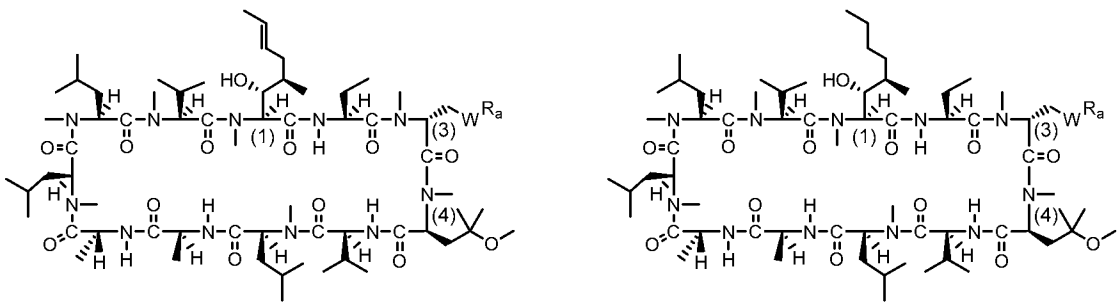
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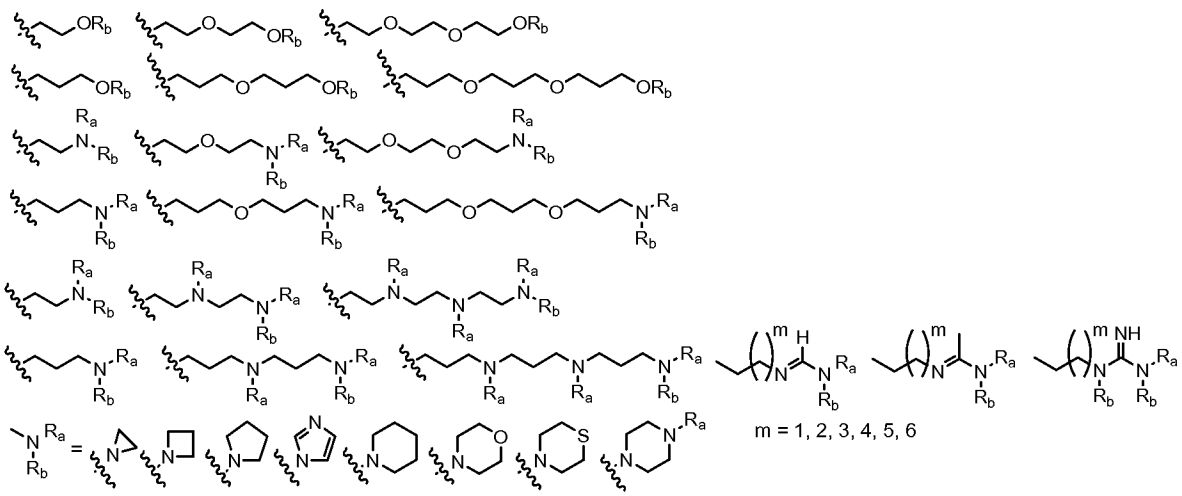




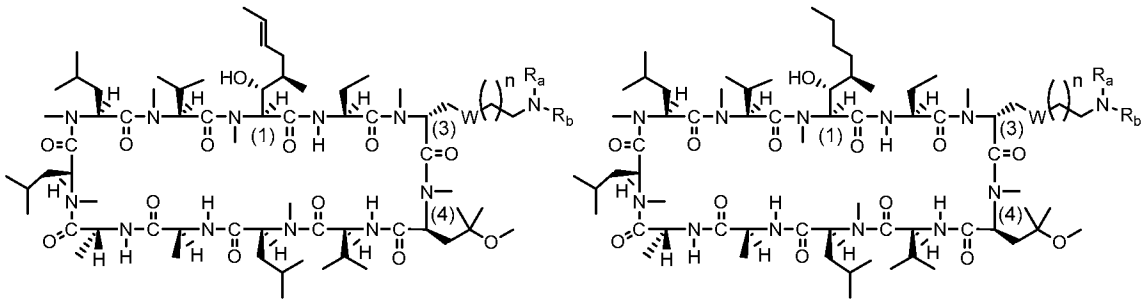
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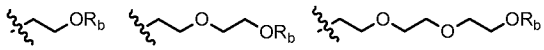
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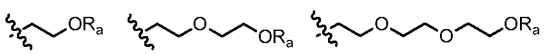
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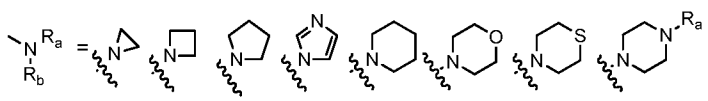
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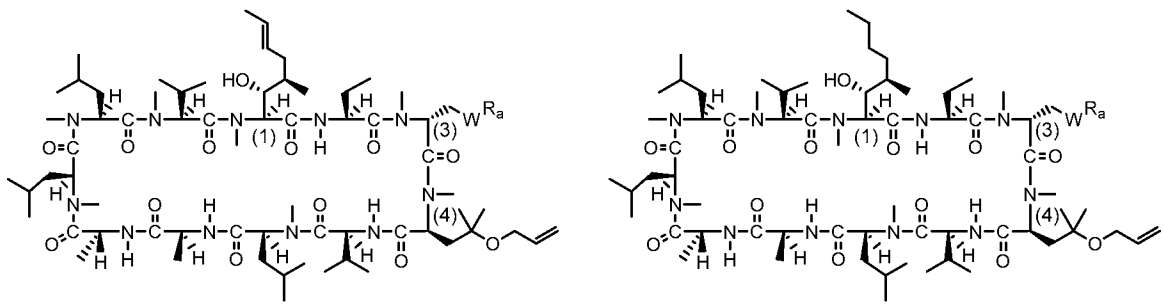
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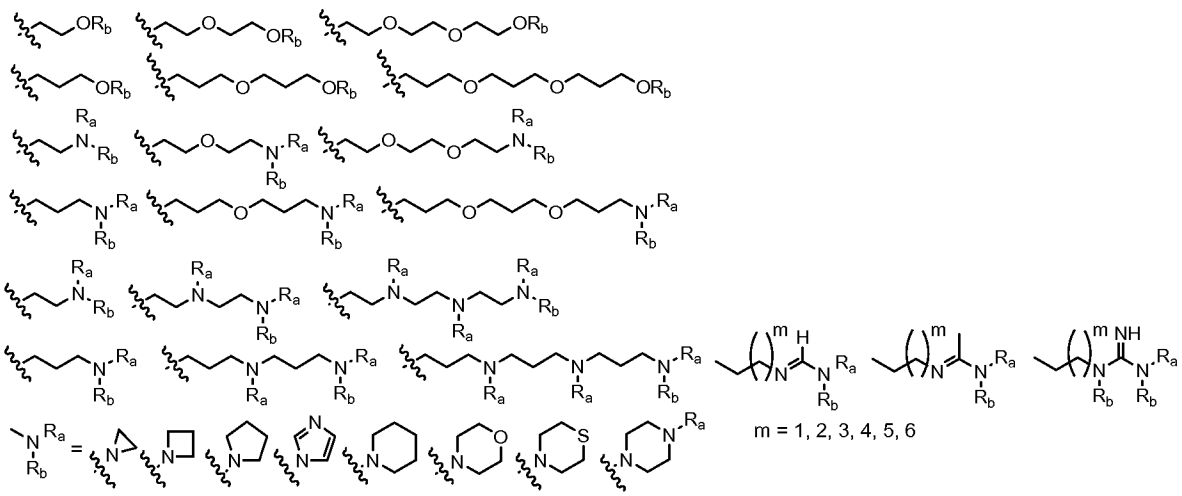




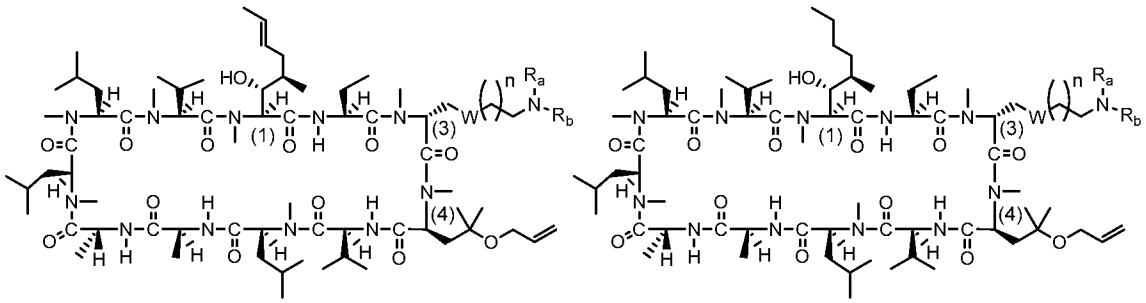
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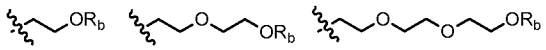
m = 1, 2, 3, 4, 5, 6



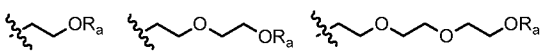
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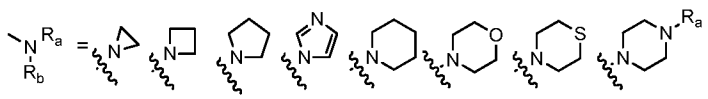
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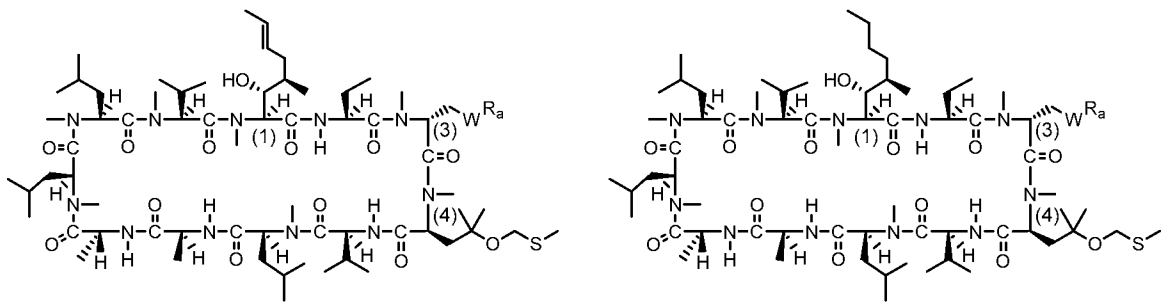
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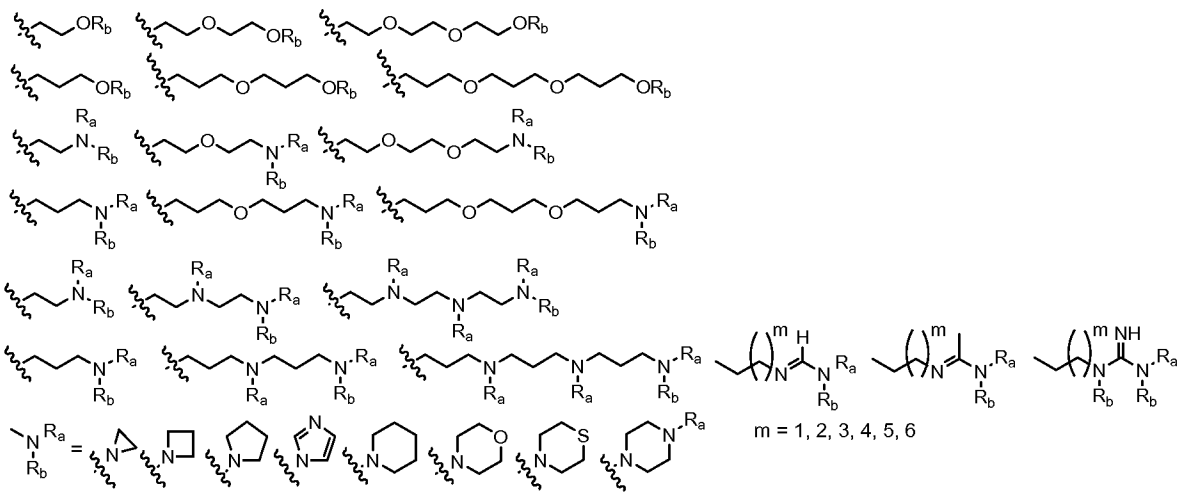




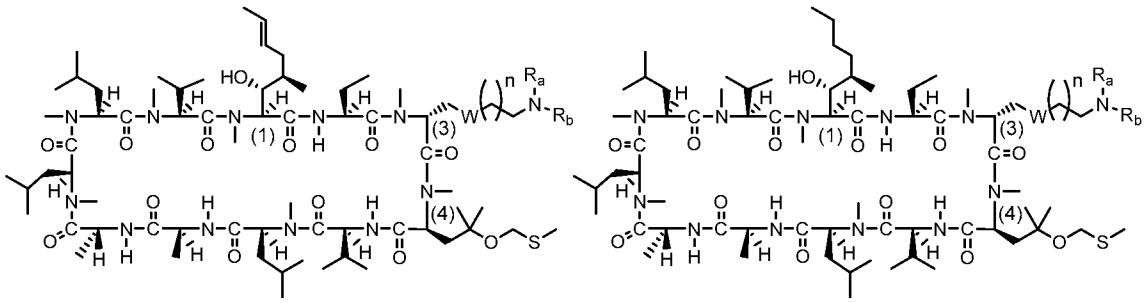
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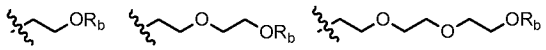
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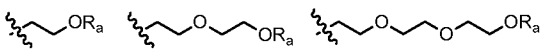
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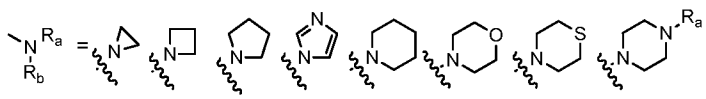
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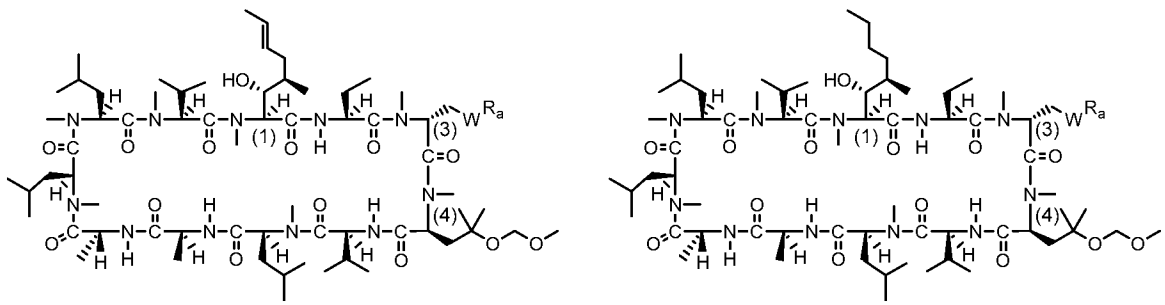
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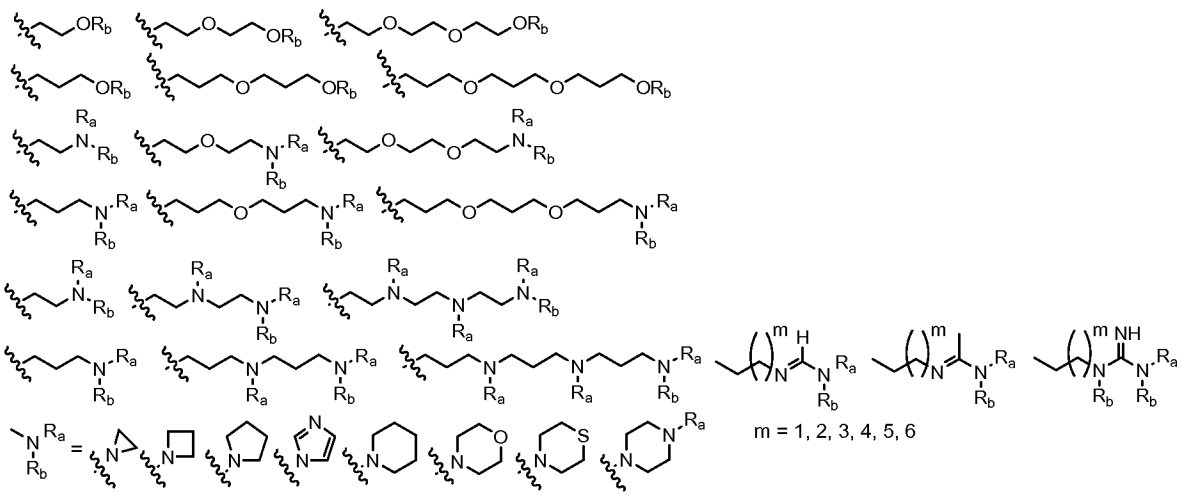




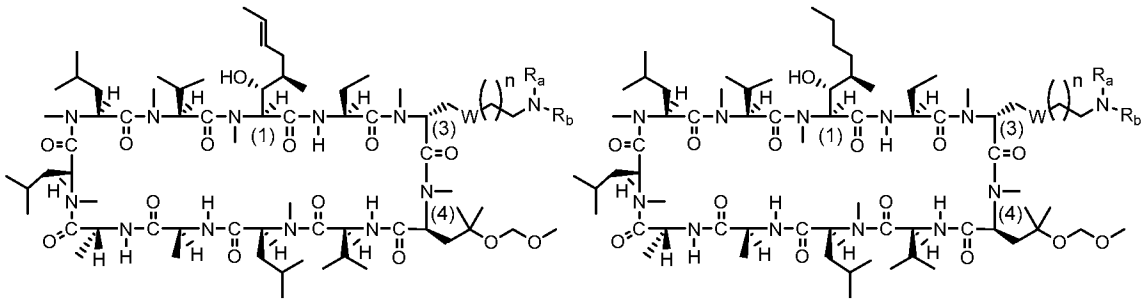
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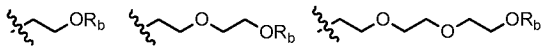
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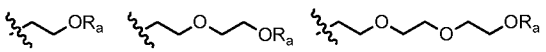
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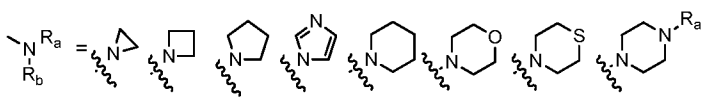
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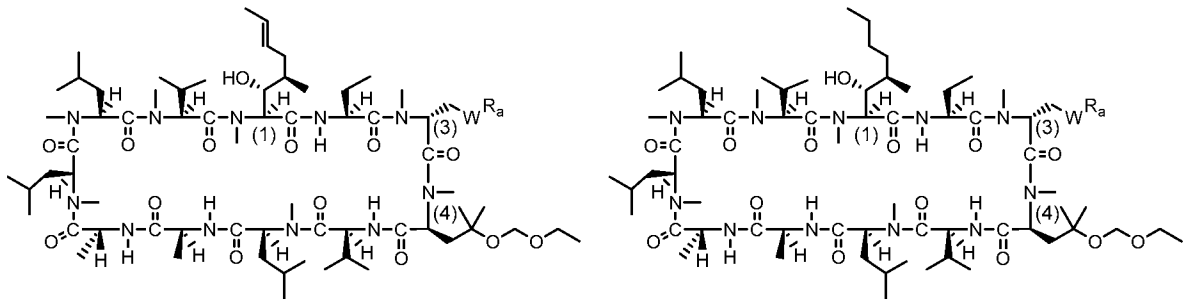
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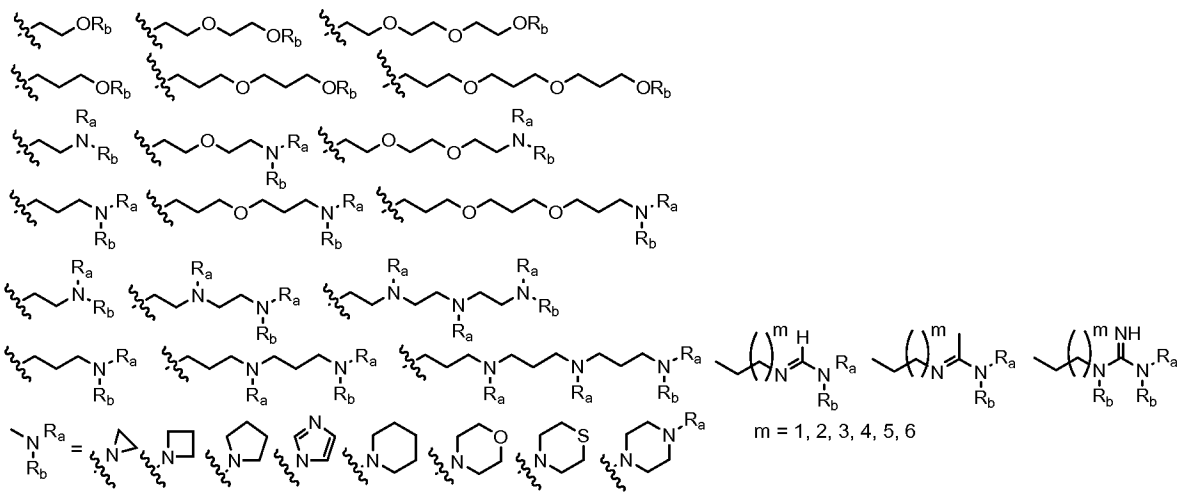




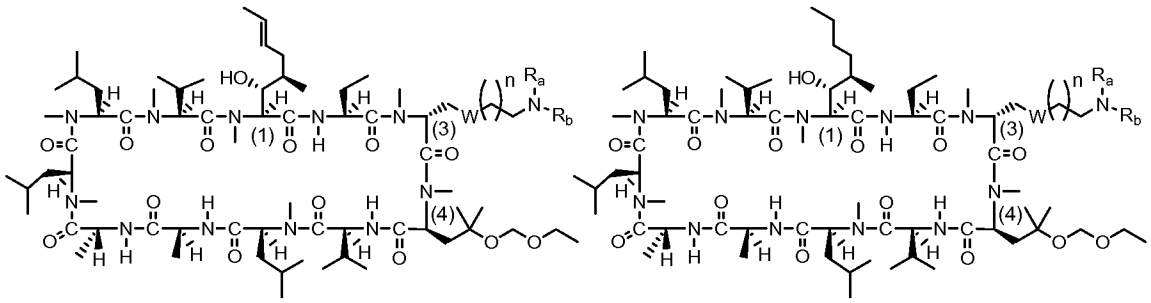
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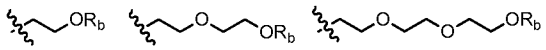
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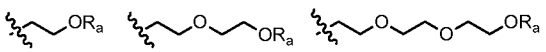
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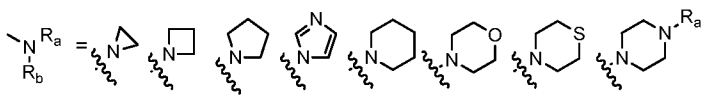
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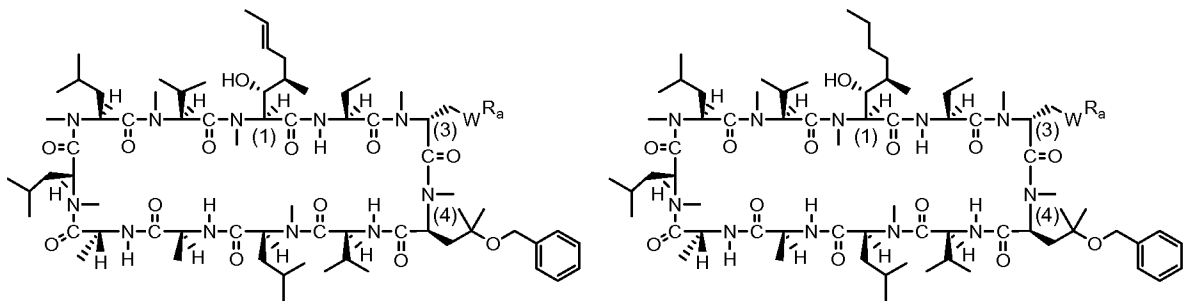
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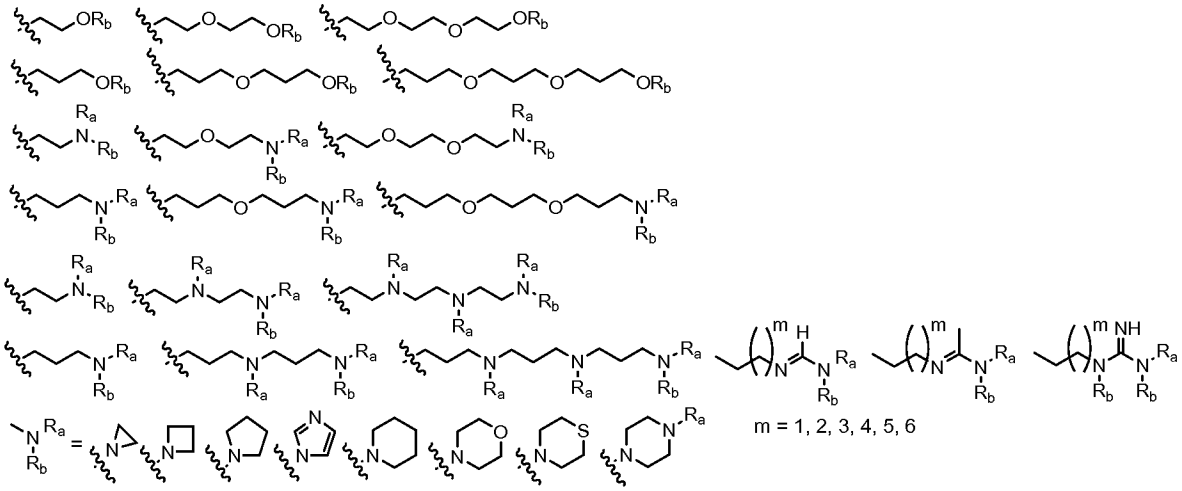




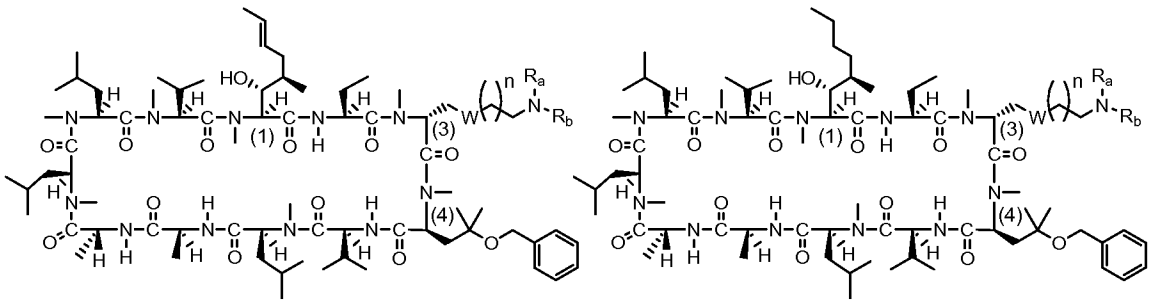
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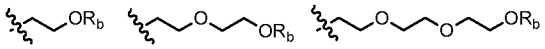
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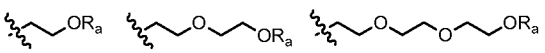
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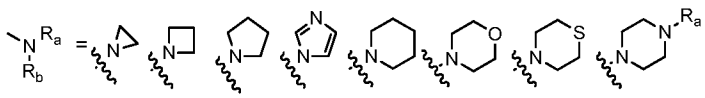
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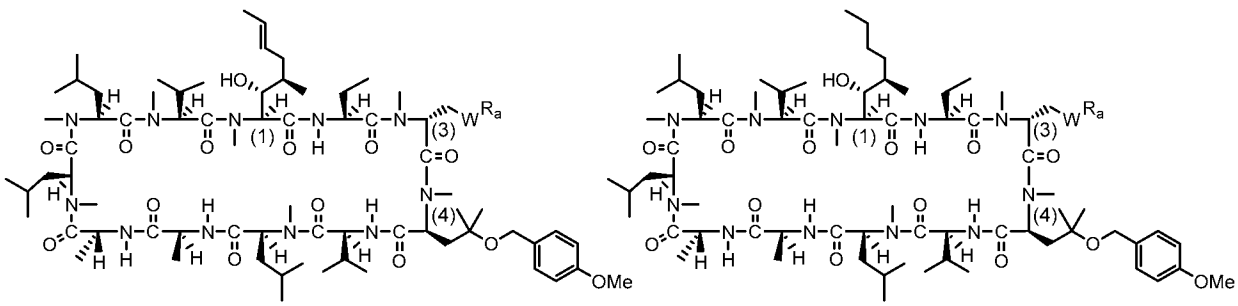
R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



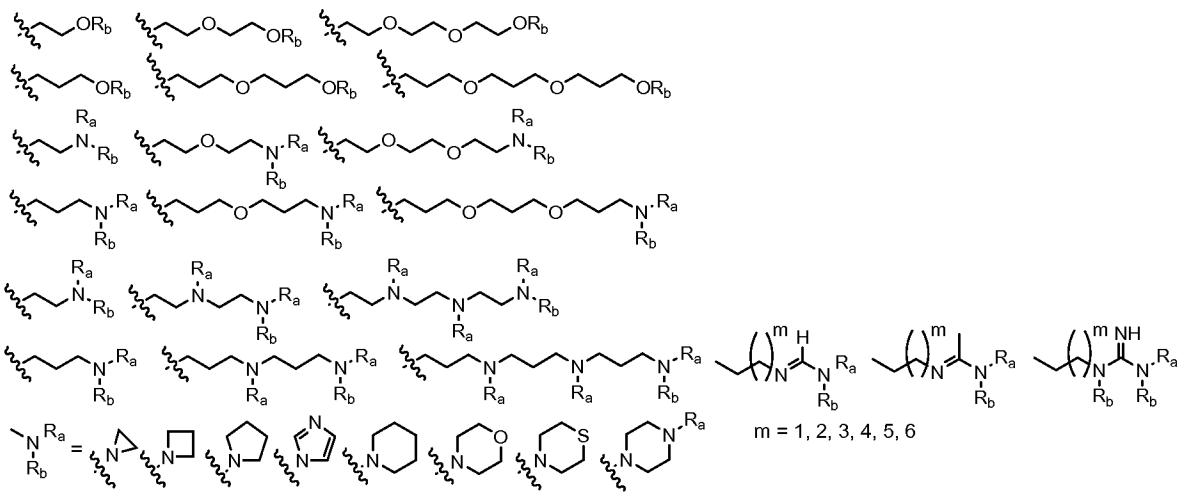




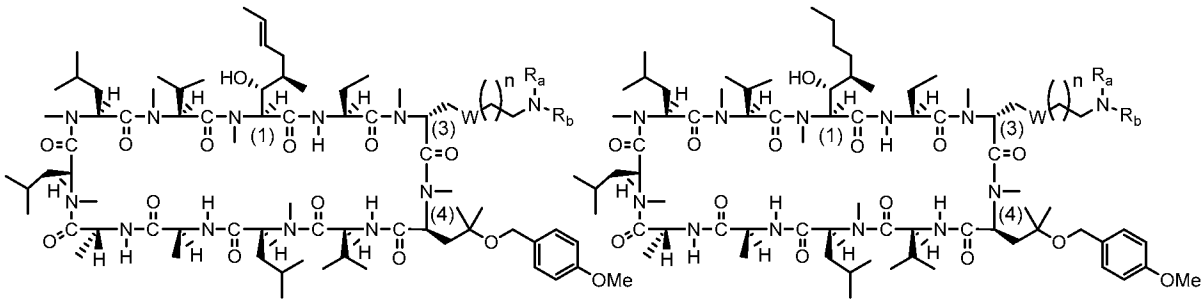
W=O, S, N-H, or N-R_a

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



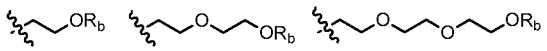
m = 1, 2, 3, 4, 5, 6



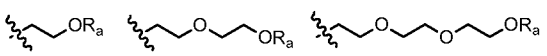
W=O, S, N-H, or N-R_a

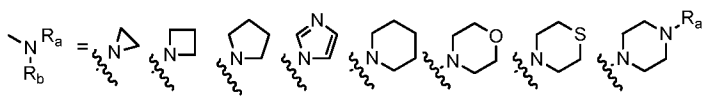
n = 6, 7, 8, 9, 10, or 11

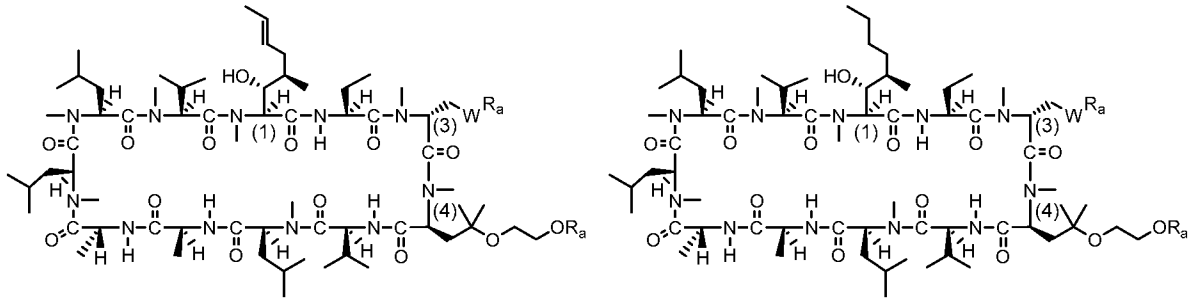
R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



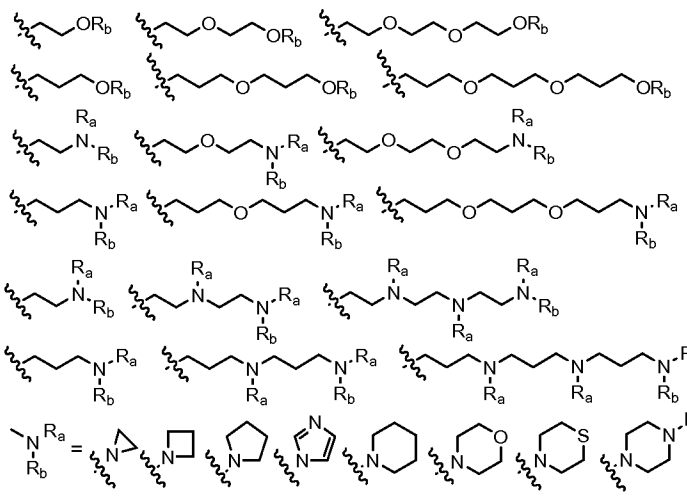




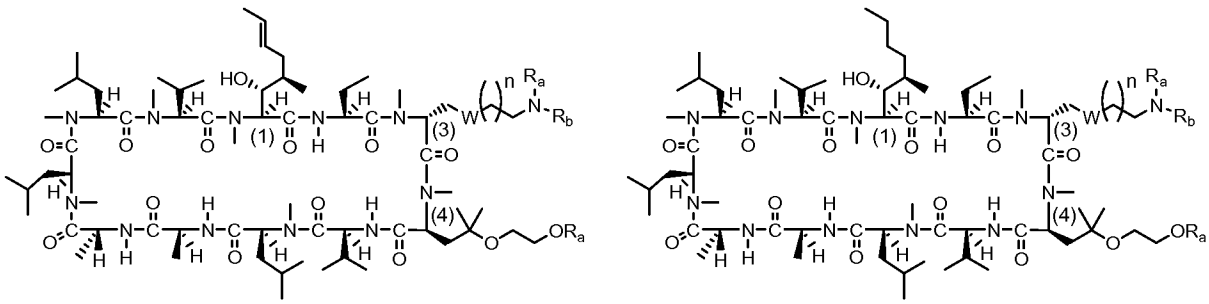
W=O, S, N-H, or N-R_a

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



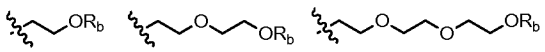
m = 1, 2, 3, 4, 5, 6



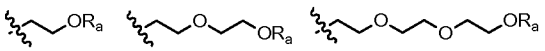
W=O, S, N-H, or N-R_a

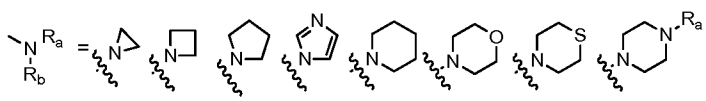
n = 6, 7, 8, 9, 10, or 11

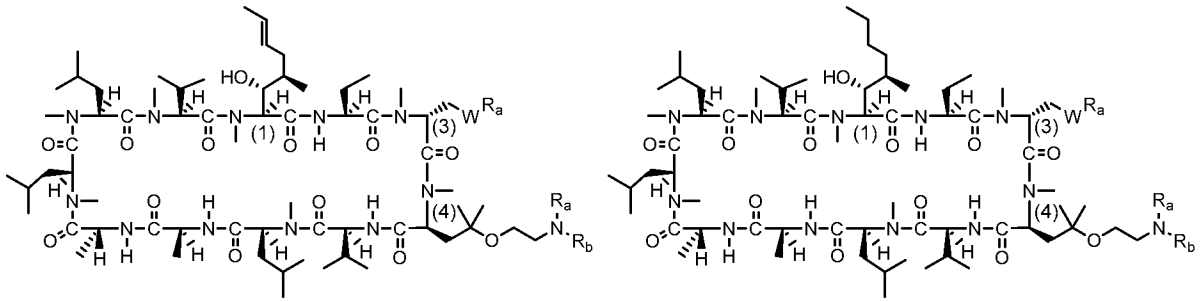
R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



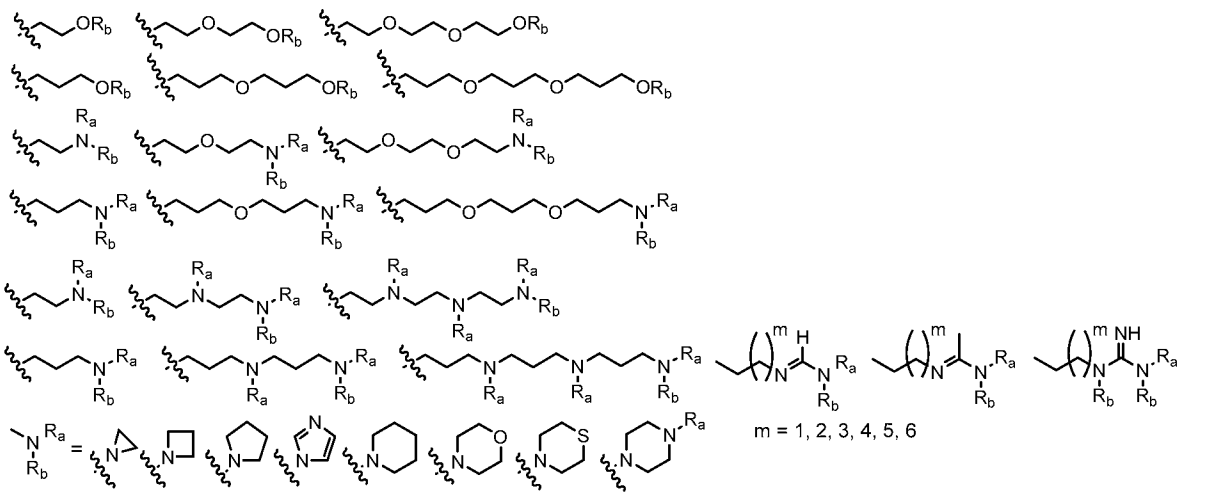




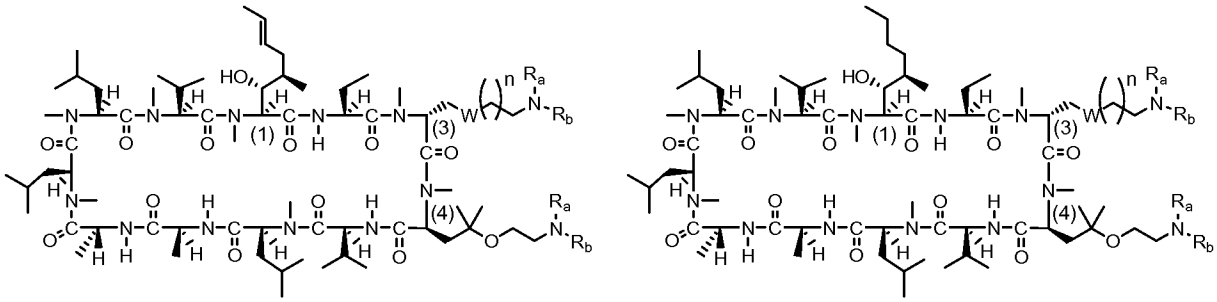
W=O, S, N-H, or N-R_a

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



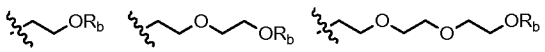
m = 1, 2, 3, 4, 5, 6



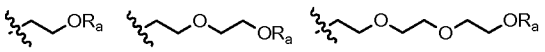
W=O, S, N-H, or N-R_a

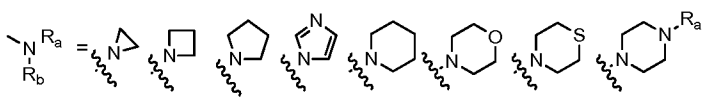
n = 6, 7, 8, 9, 10, or 11

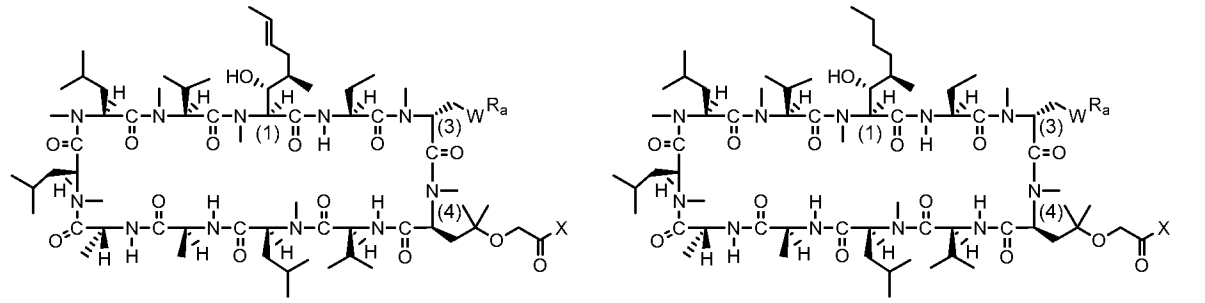
R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph





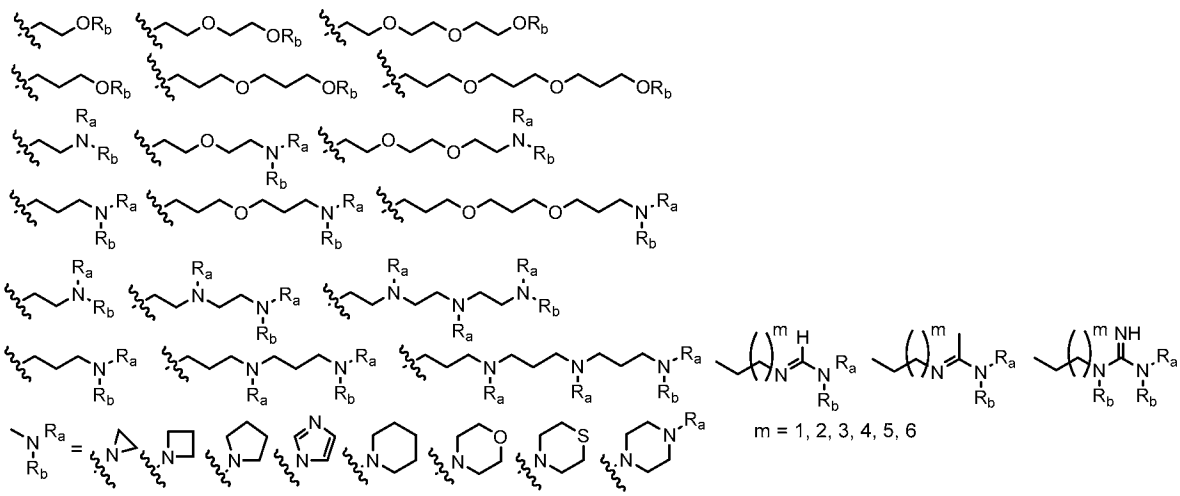


X = OH, OR_a, NR_aR_b

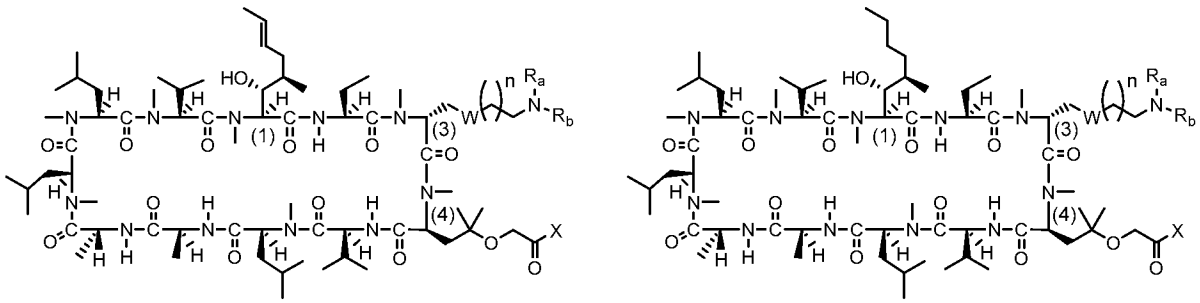
W=O, S, N-H, or N-R_a

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph

R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



m = 1, 2, 3, 4, 5, 6

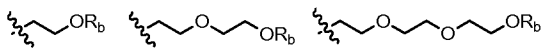


X = OH, OR_a, NR_aR_b

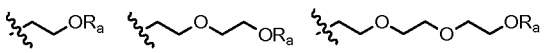
W=O, S, N-H, or N-R_a

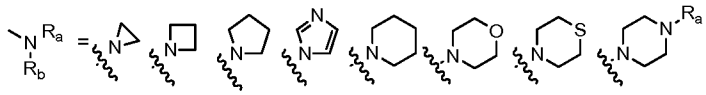
n = 6, 7, 8, 9, 10, or 11

R_a = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph



R_b = H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph





or a pharmaceutically acceptable salt thereof.

[0118] In a further aspect, the present invention provides a compound as described in the Examples.

[0119] In certain embodiments, the compounds are selected from:

[(S)-((S)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-(4-Methoxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-(4-Methoxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4-Methoxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4-Methoxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4-Methoxy-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4-Methoxy-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Methoxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Methoxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Hydroxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Hydroxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Methoxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Methoxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-(4-Methoxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-(4-Methoxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4-Methoxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4-Methoxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((S)-4-Methoxy-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-((R)-4-Methoxy-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-4-Methoxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-4-Methoxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Methoxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Methoxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Hydroxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Hydroxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-Methoxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-Methoxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-3-(Methoxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-3-(Methoxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((R)-2-(2-Methoxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

[(S)-(((S)-2-(2-Methoxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin,

or a pharmaceutically acceptable salt thereof.

[0120] In another aspect, the present invention provides a pharmaceutical composition comprising at least one compound described herein and a pharmaceutically-acceptable carrier or diluent.

[0121] In a further aspect, the present invention provides a method for treating or preventing a viral infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one

compound described herein. In certain embodiments, the viral infection is HIV infection. In certain other embodiments, the viral infection is HBV infection. In yet other embodiments, the viral infection is HCV infection. In yet other embodiments, the viral infection is influenza A virus infection, severe acute respiratory syndrome coronavirus infection or vaccinia virus infection.

[0122] In another aspect, the present invention provides a method for treating or preventing hepatitis C virus infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound described herein.

[0123] In yet another aspect, the present invention provides a method for inhibiting a cyclophilin in a subject in need thereof, which comprises administrating to said subject an effective cyclophilin-inhibiting amount of at least one compound as described herein.

[0124] In yet another aspect, the present invention provides a method for treating or preventing diseases that are mediated by cyclophilins in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein.

[0125] In yet another aspect, the present invention provides a method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the diseases are selected from inflammation, respiratory inflammation, rheumatoid arthritis, and dry eye.

[0126] In yet another aspect, the present invention provides a method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the diseases are selected from neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's Diseases, and ALS; traumatic brain injury; stroke; and ischemia-reperfusion injury in the brain, heart, and kidney.

[0127] In yet another aspect, the present invention provides a method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the diseases are selected from cardiovascular diseases, vascular stenosis, atherosclerosis, abdominal aortic aneurysms, cardiac

hypertrophy, aortic rupture, pulmonary arterial hypertension, myocarditis and myocardial fibrosis, and ischaemic heart diseases.

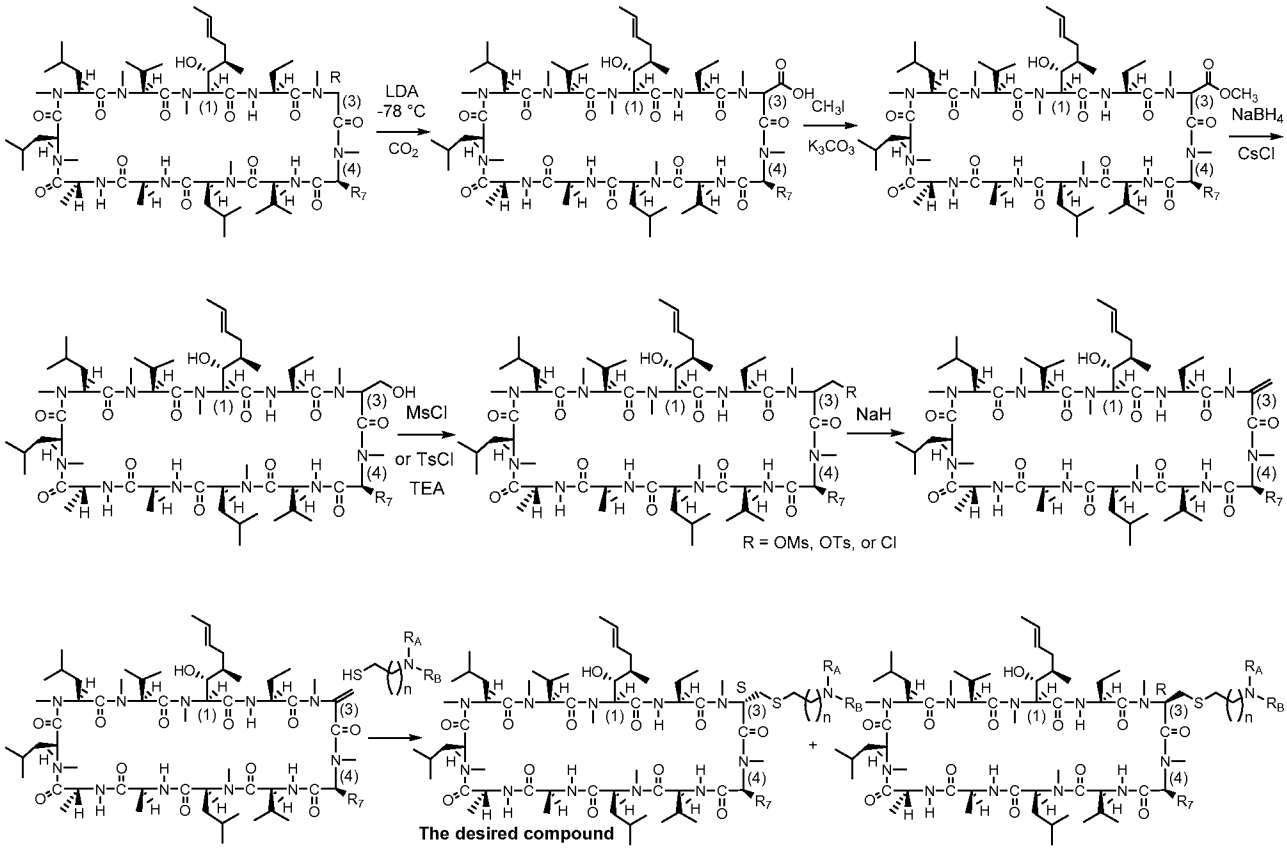
[0128] In yet another aspect, the present invention provides a method for treating or preventing diseases or conditions in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the diseases or conditions are selected from cancer, obesity, diabetes, muscular dystrophy, and hair loss.

[0129] In yet another aspect, the present invention provides a method for treating or preventing diseases or conditions in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound as described herein, wherein the diseases or conditions are selected from allergic conjunctivitis, atopic and vernal keratoconjunctivitis, atopic keratoconjunctivitis, anterior uveitis, Behcet's disease, blepharitis, chronic ocular surface inflammation caused by viral infection, corneal transplant rejection, corneal sensitivity impaired due to surgery on the cornea or other surface of the eye, meibomian gland disease, ptyregia, ocular symptoms of graft versus host disease, ocular allergy, ocular cicatricial pemphigoid, Steven Johnson syndrome, vernal keratoconjunctivitis, uveitis, herpes simplex keratitis, ocular rosacea, and Pinguecula.

Methods of Preparation

[0130] In certain embodiments, the compound of formulae (I) and (II) can be prepared by treating cyclosporin A or an analog thereof with a base (*e.g.*, LDA) to form a sarcosine enolate at 3-position, and then CO_2 gas is introduced to yield carboxylic acid-3-cyclosporin, after formation of its corresponding methyl ester and reduction of the methyl ester side chain to alcohol, its mesylate, tosylate or chloride can be formed by treatment with MsCl or TsCl in dichloromethane solution, and they can be converted to the methylene on the sarcosine by treatment with a base (*e.g.*, NaH), when sulfur nuclectrophile is used for 1,4-addition reaction on the methylene group, the methylene sulfur side chain with S-conformation can be formed on the sarcosine of position 3 as novel cyclosporine derivatives. For example:

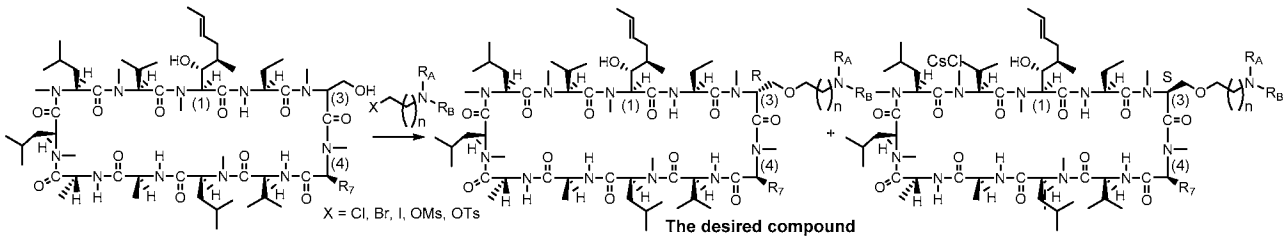
Scheme 1



[0131] [α-Methylene-Sar]-3-cyclosporin also was prepared using a method analogous to the procedure described in WO2012/051194A1 (which is incorporated herein by reference).

[0132] In certain embodiments, the above resulting alcohol can be converted to its methylene oxygen ether side chain to form novel cyclosporine derivatives too. For example:

Scheme 2



[0133] In Schemes 1-2 above, the symbols have the same meaning as defined in the claims and throughout the specification, unless otherwise noted.

[0134] In certain other embodiments, the compound of formula I-VI, IIa-VIa, IIb-VIb, IIc-IVc can be obtained according to the procedures described herein.

Pharmaceutical Compositions

[0135] This invention also provides a pharmaceutical composition comprising at least one of the compounds as described herein or a pharmaceutically-acceptable salt or solvate thereof, and a pharmaceutically-acceptable carrier.

[0136] The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as butylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0137] As set out above, certain embodiments of the present pharmaceutical agents may be provided in the form of pharmaceutically-acceptable salts. The term "pharmaceutically-acceptable salt", in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge *et al.*, (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

[0138] The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, butionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[0139] In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge *et al.*, supra)

[0140] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate, magnesium stearate, and polyethylene oxide-polybutylene oxide copolymer as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0141] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated and the particular mode of administration. The

amount of active ingredient, which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of 100%, this amount will range from about 1% to about 99% of active ingredient, preferably from about 5% to about 70%, most preferably from about 10% to about 30%.

[0142] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0143] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[0144] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium carbonate, and sodium starch glycolate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and polyethylene oxide-polybutylene oxide copolymer; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also

comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0145] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxybutylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets, may be, made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0146] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxybutylmethyl cellulose in varying butortions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions, which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples are embedding compositions, which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if apbutriate, with one or more of the above-described excipients.

[0147] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isobutyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, butylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures

thereof. Additionally, cyclodextrins, e.g., hydroxybutyl-.beta.-cyclodextrin, may be used to solubilize compounds.

[0148] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0149] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0150] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active pharmaceutical agents of the invention.

[0151] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be apbutriate.

[0152] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or butellants which may be required.

[0153] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0154] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary butellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and butane.

[0155] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving, or dispersing the pharmaceutical agents in the buter medium. Absorption enhancers can also be used to increase the flux of the pharmaceutical agents of the invention across the skin. The rate of such flux can be controlled, by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0156] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[0157] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0158] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. One strategy for depot injections includes the use of polyethylene oxide-polybutylene oxide copolymers wherein the vehicle is fluid at room temperature and solidifies at body temperature.

[0159] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly (orthoesters) and poly (anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions, which are compatible with body tissue.

[0160] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical

composition containing, for example, 0.1% to 99.5% (more preferably, 0.5% to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[0161] The compounds and pharmaceutical compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutical compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, the compound of the present invention may be administered concurrently with another anti-HCV agent), or they may achieve different effects (e.g., control of any adverse effects).

[0162] The compounds of the invention may be administered intravenously, intramuscularly, intraperitoneally, subcutaneously, topically, orally, or by other acceptable means. The compounds may be used to treat arthritic conditions in mammals (i.e., humans, livestock, and domestic animals), birds, lizards, and any other organism, which can tolerate the compounds.

[0163] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Equivalents

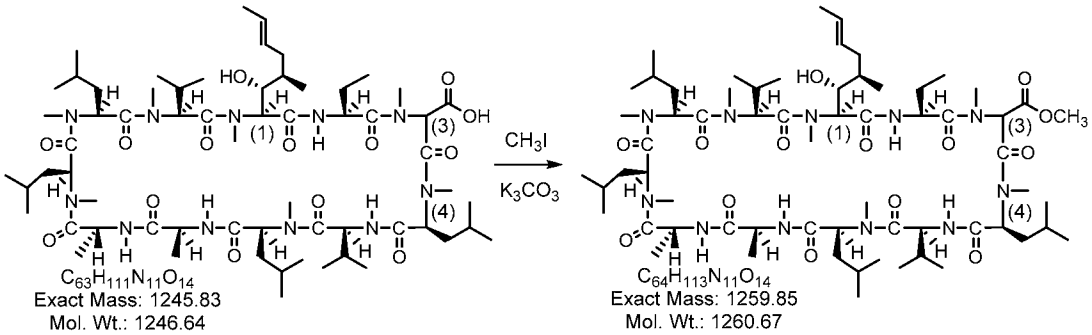
[0164] The representative examples which follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. It should further be appreciated that the contents of those cited references are incorporated herein by reference to help illustrate the state of the art. The following examples contain important

additional information, exemplification and guidance which can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

Examples

Example 1

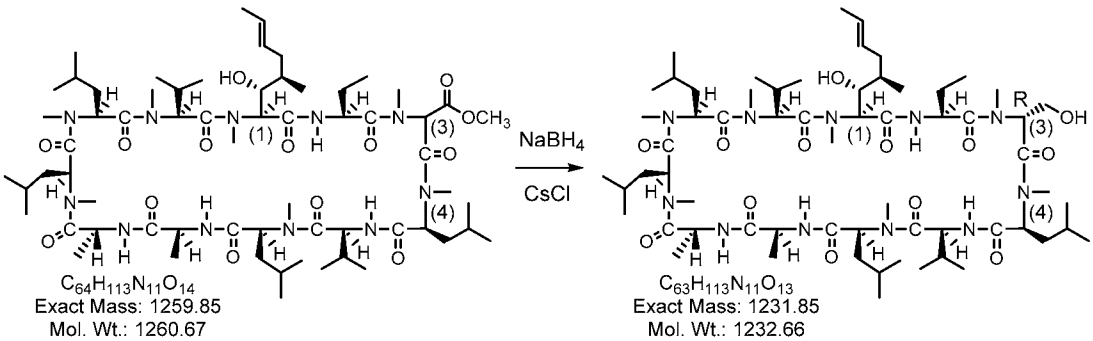
[α-Methoxycarbonyl-Sar]-3-cyclosporin



[0165] [α-Carboxy-sar]-3-cyclosporin (5.00 g, 4.01 mmol) was dissolved in N,N-dimethylformamide (30 ml). Iodomethane (2.85 g, 20.10 mmol) and potassium carbonate (1.38 g, 10.00 mmol) were added. The mixture was stirred at room temperature for 2 hours. Then ethyl acetate (60 ml) and water (60 ml) were added and the mixture was separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 5.32 g of crude product, which was directly used for the next step without purification (yield: ~ 100%) [Molecular Formula: $C_{64}H_{113}N_{11}O_{14}$; Exact Mass: 1259.85; MS (m/z): 1260.7 $(M+1)^+$, 1282.7 $(M+Na)^+$; TLC R_f: 0.55 (dichloromethane/methanol = 9/1)].

Example 2

[(R)-α-Hydroxymethyl-Sar]-3-cyclosporin

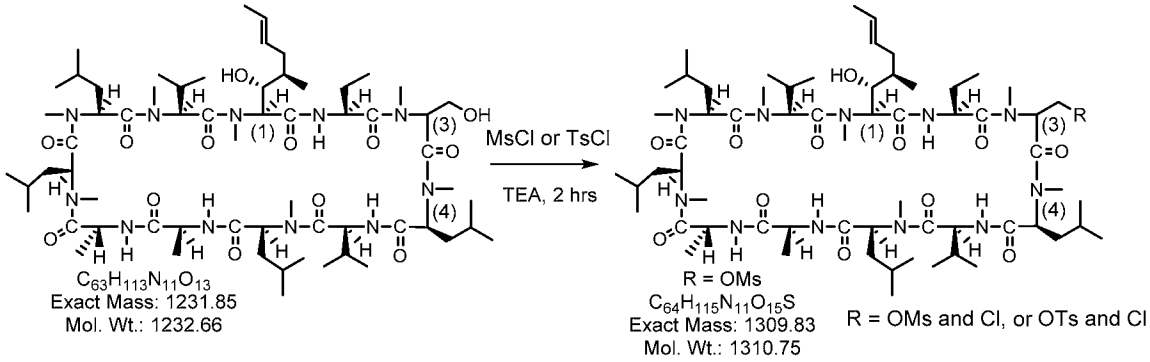


[0166] [α-Methoxycarbonyl-Sar]-3-cyclosporin (2.00 g, 1.59 mmol) was dissolved in tetrahydrofuran (30 ml). Cesium chloride (1.33 g, 7.90 mmol) and sodium borohydride (0.60 g, 15.89 mmol) were added in portions. Then methanol (30 ml) was added dropwise to the mixture over 2 hours. After addition, the mixture was stirred at room temperature

overnight. Most of solvent was then evaporated under reduced pressure. Ethyl acetate (50 ml) and water (50 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 1.99 g of crude product, which was purified by on silica gel column with dichloromethane/methanol (from 100:0 to 95:5) to give the 1.50 g of pure product (yield: 76%) [Molecular Formula: $C_{63}H_{113}N_{11}O_{13}$; Exact Mass: 1231.85; MS (m/z): 1232.7 $(M+1)^+$, 1254.7 $(M+Na)^+$].

Example 3

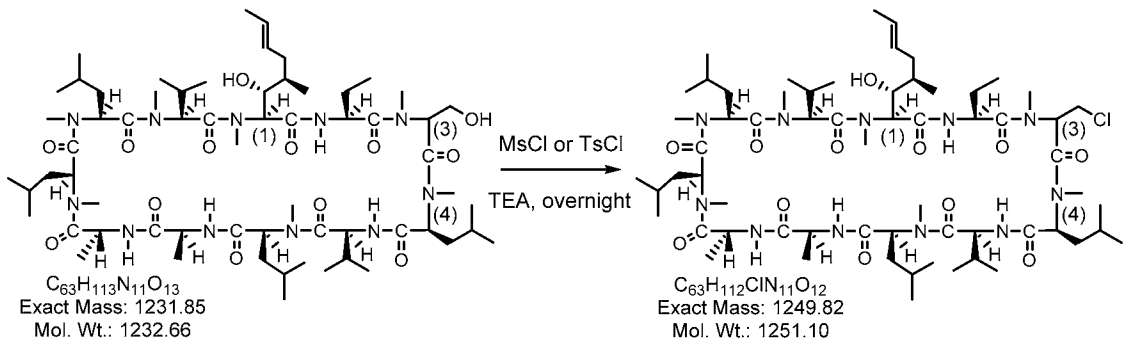
[α-Methylmethanesulfonate-Sar]-3-cyclosporin



[0167] To a solution of [α-hydroxymethyl-Sar]-3-cyclosporin (30 mg, 0.024 mmol) in dichloromethane (2 ml) at 0 °C were added triethylamine (52.8 µl, 0.38 mmol), and methanesulfonyl chloride (23 mg, 0.20 mmol). The mixture was stirred at room temperature for two hours. Then reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 33 mg of crude product, which was directly used in next step reaction without further purification [Molecular Formula: $C_{64}H_{115}N_{11}O_{15}S$; Exact Mass: 1309.83; MS (m/z): 1310.7 $(M+1)^+$].

Example 4

[α-Chloromethyl-Sar]-3-cyclosporin

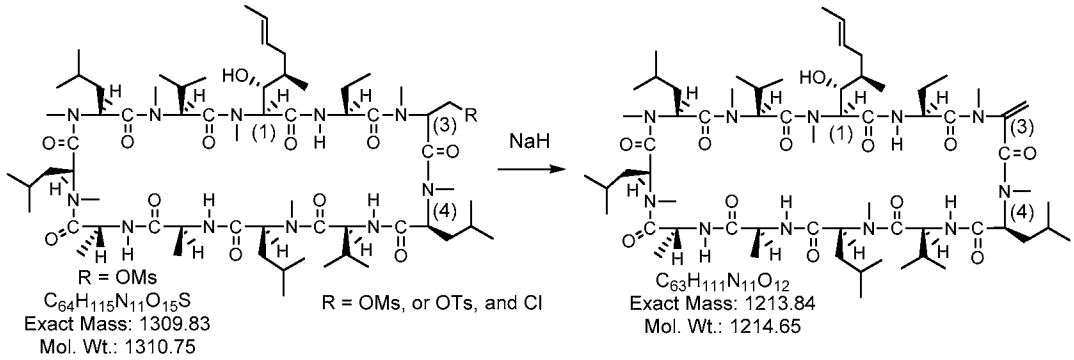


[0168] To a solution of [α-hydroxymethyl-Sar]-3-cyclosporin (30 mg, 0.024 mmol) in dichloromethane (2 ml) at 0 °C were added triethylamine (52.8 μL, 0.384 mmol, 16 equivalents) and methanesulfonyl chloride (23 mg, 0.20 mmol). The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 30 mg of crude product, which was directly used in next step reaction without further purification [Molecular Formula: $C_{63}H_{112}ClN_{11}O_{12}$; Exact Mass: 1249.82; MS (m/z): 1250.7 $(M+1)^+$, 1272.9 $(M+Na)^+$].

Example 5

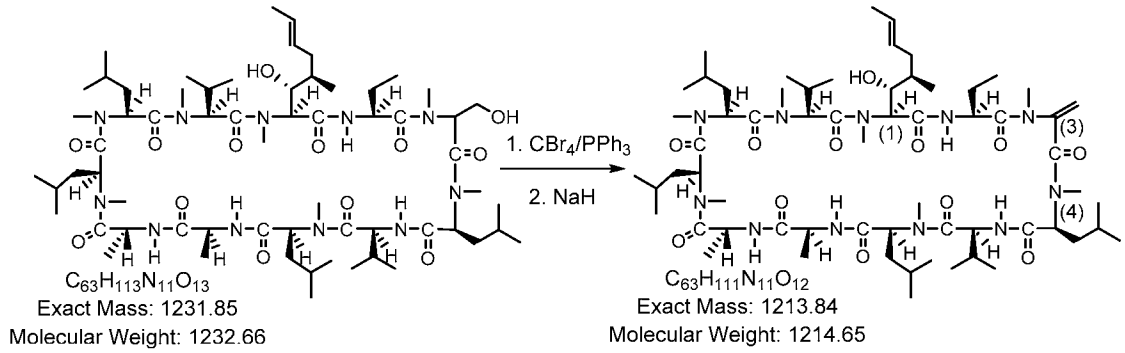
[α-Methylene-Sar]-3-cyclosporin

Method 1



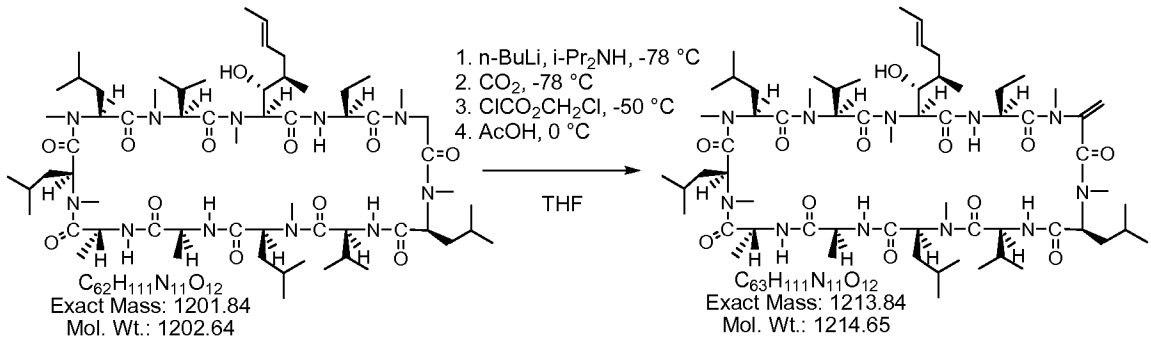
[0169] To a solution of either [α-methanesulfonatemethyl-Sar]-3-cyclosporin (33 mg, 0.025 mmol) or [α-chloromethyl-Sar]-3-cyclosporin (30 mg, 0.025 mmol) in tetrahydrofuran (3 ml) was added sodium hydride (15.3 mg, 60% in oil, 0.38 mmol, 10 equivalents) at 0 °C. The mixture was stirred at 0 °C for one hour and then warmed up to room temperature for 30 minutes. After removal of solvent, the residue was dissolved in dichloromethane (20 ml). The dichloromethane layer was washed with 1 N hydrochloric acid, saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethylene/methanol (20/1) to give 16 mg of product (yield: 54%) [Molecular Formula: $C_{63}H_{111}N_{11}O_{12}$; Exact Mass: 1213.84; MS (m/z): 1214.7 $(M+1)^+$, 1236.7 $(M+Na)^+$; TLC R_f: 0.55 (ethyl acetate/methanol = 20/1); HPLC RT: 7.0 min (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Method 2



[0170] [(R)-α-Hydroxymethyl-Sar]-3-cyclosporin (100 mg, 0.08 mmol), carbon tetrabromide (135mg, 0.40 mmol) and triphenylphosphine (106 mg, 0.40 mmol) were dissolved in dichloromethane (5 ml). The mixture was stirred under nitrogen at room temperature for two hours. Then the mixture was added into a suspension of sodium hydride (60% dispersion in mineral oil) (20 mg, 0.50 mmol) in tetrahydrofuran (3 ml) under nitrogen at 0 °C. The mixture was stirred at 0 °C for five hours. Most of solvents then were evaporated under reduced pressure. Ethyl acetate (20 ml) and water (30 ml) were added and the mixture was separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography to give a product of [α-methylene-Sar]-3-cyclosporin [Molecular Formula: $C_{63}H_{111}N_{11}O_{12}$; Exact Mass: 1213.84; MS (m/z): 1214.70 $(M+1)^+$, 1236.70 $(M+Na)^+$; HPLC RT: 17.83 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

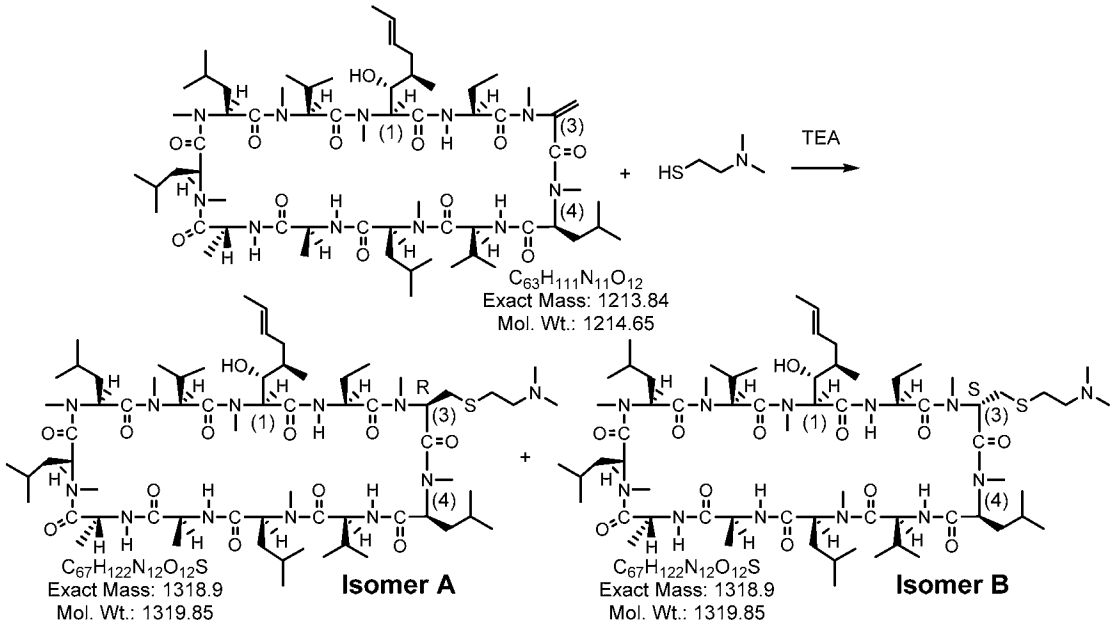
Method 3



[0171] [α-Methylene-Sar]-3-cyclosporin was prepared by a method according to the procedure described in WO2012/051194A1 (which is incorporated herein by reference).

Example 6

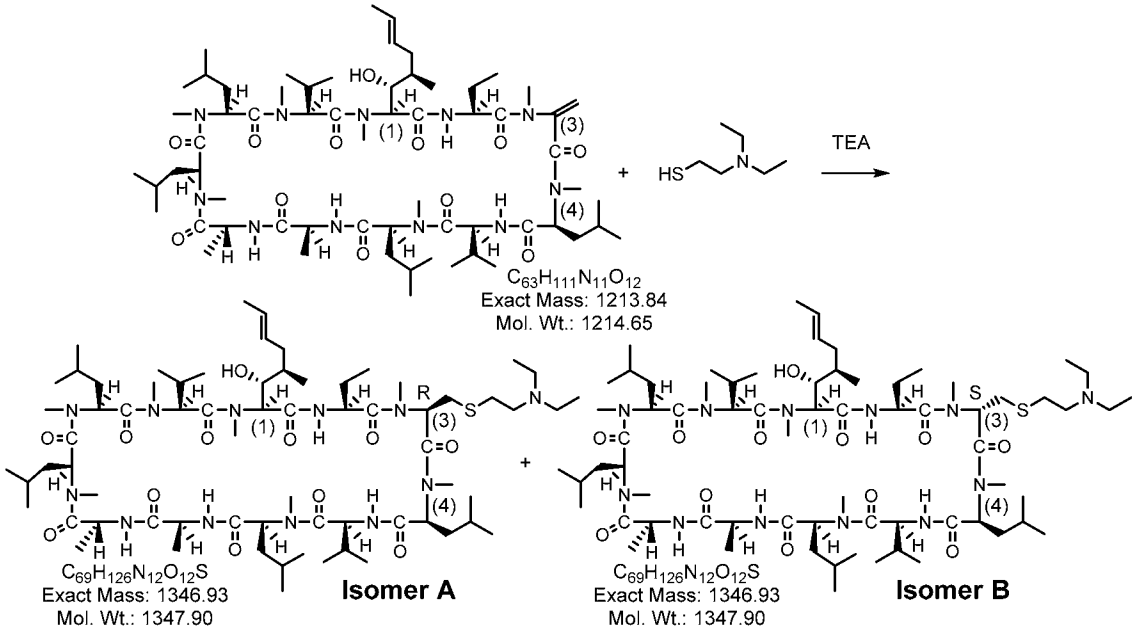
[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-cyclosporin (Isomer B) and [(R)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-cyclosporin (Isomer A)



[0172] To a solution of [α-methylene-Sar]-3-cyclosporine (0.60 g, 0.50 mmol) and 2-(dimethylamino)ethanethiol (0.63 g, 6.00 mmol) in methanol (20 ml) was added triethylamine (0.82 ml, 6.0 mmol). The reaction mixture was stirred overnight at room temperature. After removal of solvent, the residue was subjected to chromatography using dichloromethane /methanol as eluent to give 0.35 g of (R)-2-(N,N-dimethylamino)ethylthiomethyl-Sar]-3-cyclosporin (isomer A) and 0.20 g of [(S)-2-(N,N-dimethylamino)ethylthiomethyl-Sar]-3-cyclosporin (isomer B) [Molecular Formula: $C_{67}H_{122}N_{12}O_{12}S$; Exact Mass: 1218.9; MS (m/z): 1319.80 $(M+1)^+$; TLC R_f: 0.20 (ethyl acetate/methanol = 5/1); HPLC RT: 12.55 min (isomer A) and 13.22 min (isomer B) (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 7

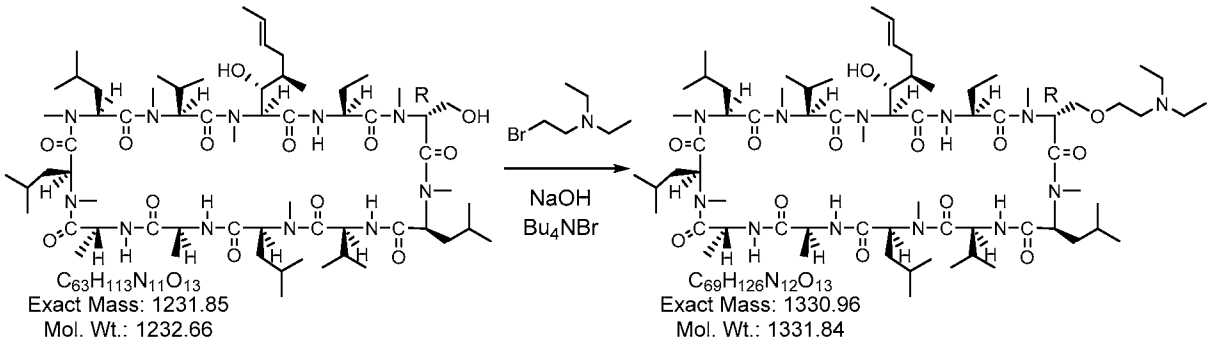
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-cyclosporin (Isomer B) and [(R)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-cyclosporin (Isomer A)



[0173] To a solution of [α-methylene-Sar]-3-cyclosporin (0.31 g, 0.25 mmol) and 2-diethylaminoethanethiol (0.40 g, 3.00 mmol) in methanol (10 ml) was added triethylamine (0.41 ml, 3.00 mmol, 12 equivalents). The reaction mixture was stirred overnight at room temperature. After removal of solvent, the residue was subjected to chromatography using dichloromethane /methanol as eluent to yield 0.20 g of [(R)-2-(N,N-Diethylamino)ethylthiomethyl-Sar]-3-cyclosporin (isomer A) and 0.08 g of [(S)-2-(N,N-Diethylamino)ethylthiomethyl-Sar]-3-cyclosporin (isomer B) [Molecular Formula: $C_{69}H_{126}N_{12}O_{12}S$; Exact Mass: 1346.93; MS (m/z): 1347.80 $(M+1)^+$; TLC R_f: 0.23 (ethyl acetate/methanol = 5/1); HPLC RT: 13.37 min (isomer A) and 13.91 min (isomer B) (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 8

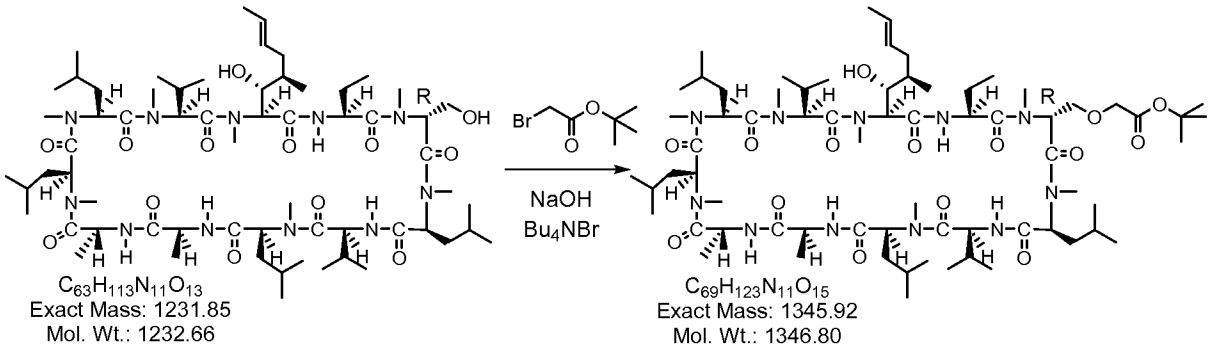
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-cyclosporin



[0174] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (0.36 g, 0.29 mmol) in benzene (30 ml) were added a solution of sodium hydroxide (1.20 g, 30 mmol) in water (2 ml), 2-bromo-N,N-diethylethylamine hydrobromide (3.80 g, 14.56 mmol) and tetra-n-butylammonium bromide(0.20 g, 0.62 mmol). The reaction mixture was stirred at 30 °C for 20 hours. After diluted with ice water, the mixture was separated. The aqueous layer was extracted with dichloromethane (30 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 210 mg of product [Molecular Formula: $C_{69}H_{126}N_{12}O_{13}$; Exact Mass: 1330.96; MS (m/z): 1331.71$(M+1)^+$; TLC R_f: 0.38 (dichloromethane/methanol = 95/5); HPLC RT: 14.12 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 9

[(R)-(tert-Butoxycarbonylmethoxy)methyl-Sar]-3-cyclosporin

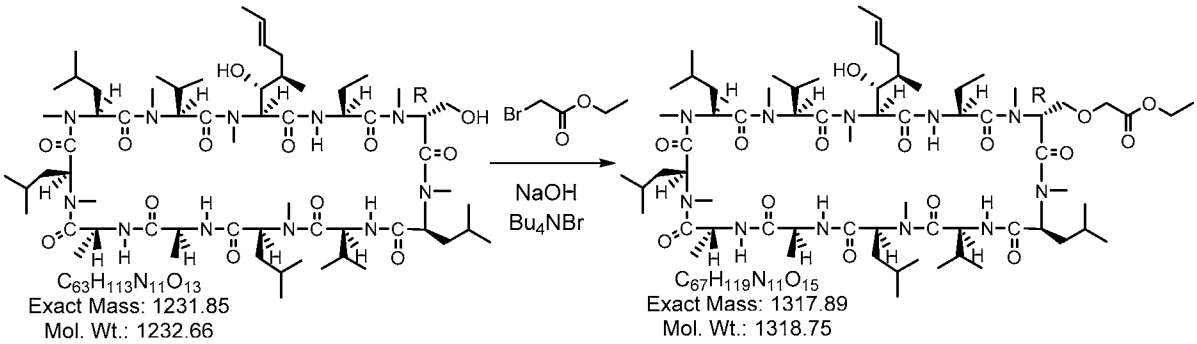


[0175] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (0.50 g, 0.41 mmol) in benzene (30 ml) were added a solution of sodium hydroxide (1.00 g, 25.00 mmol) in water (1 ml), t-butyl bromoacetate (3.20 g, 16.41 mmol) and tetra-n-butylammonium bromide (0.40 g, 1.24 mmol). The mixture was stirred at room temperature for 10 hours.

After diluted with ice water, the mixture was separated. The aqueous layer was extracted with dichloromethane (30 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone = 2/1) to give 0.41 g product [Molecular Formula: $C_{69}H_{123}N_{11}O_{15}$; Exact Mass: 1345.92; MS (m/z): 1346.61 $(M+1)^+$; TLC R_f: 0.60 (dichloromethane/methanol = 95/5); HPLC RT: 18.29 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 10

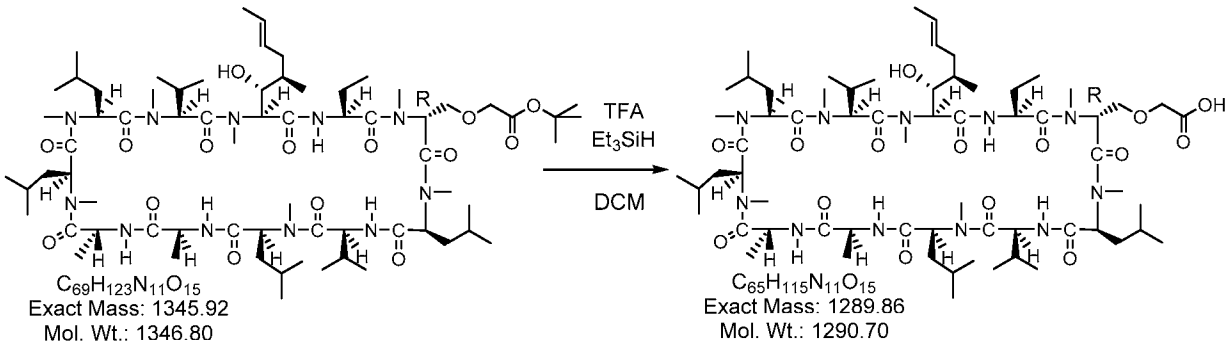
[(R)-(Ethoxycarbonylmethoxy)methyl-Sar]-3-cyclosporin



[0176] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (0.35 g, 0.28 mmol) in benzene (15 ml) were added a solution of sodium hydroxide (0.60 g, 15.00 mmol) in water (1 ml), ethyl bromoacetate (1.60 g, 9.58 mmol) and tetra-n-butylammonium bromide (0.20 g, 0.62 mmol). The mixture was stirred at room temperature for 10 hours. After diluted with ice water, the mixture was separated. The aqueous layer was extracted with dichloromethane (15 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone = 2/1) to give 0.31 g of product [Molecular Formula: $C_{67}H_{119}N_{11}O_{15}$; Exact Mass: 1317.89; MS (m/z): 1318.46 $(M+1)^+$; TLC R_f: 0.55 (dichloromethane/methanol = 95/5); HPLC RT: 17.40 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 11

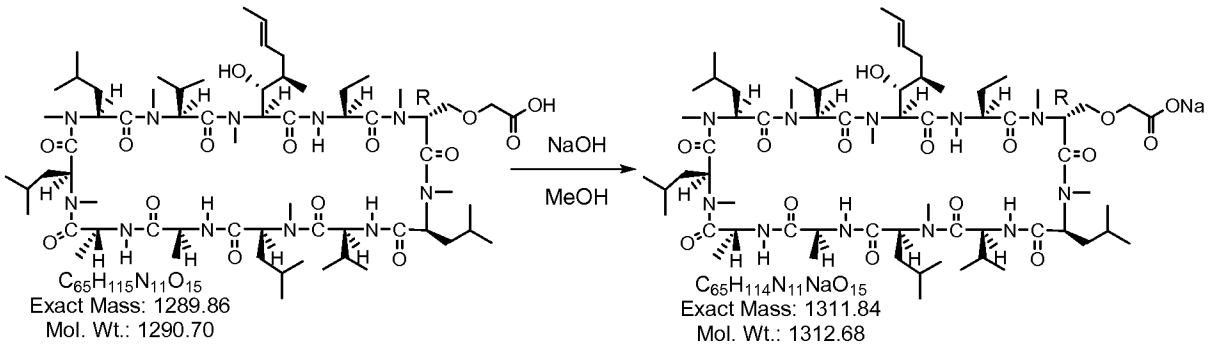
[(R)-(Carboxymethoxy)methyl-Sar]-3-cyclosporin



[0177] To a solution of [(R)-((tert-butoxycarbonyl)methoxy)methyl-Sar]-3-cyclosporin (0.18 g, 0.13 mmol) in dichloromethane (5 ml) were added trifuloroacetic acid (1 ml) and triethylsilane (10 drops). The mixture was stirred at room temperature for 3 hours and concentrated under reduced pressure. Then dichloromethane (10 ml) and water (10 ml) were added and the mixture was separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by C-18 chromatography (acetonitrile/water) to give 75 mg of product [Molecular Formula: $C_{65}H_{115}N_{11}O_{15}$; Exact Mass: 1289.86; MS (m/z): 1290.56 $(M+1)^+$; HPLC RT: 11.03 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 12

[(R)-(Carboxymethoxy)methyl-Sar]-3-cyclosporin-sodium salt

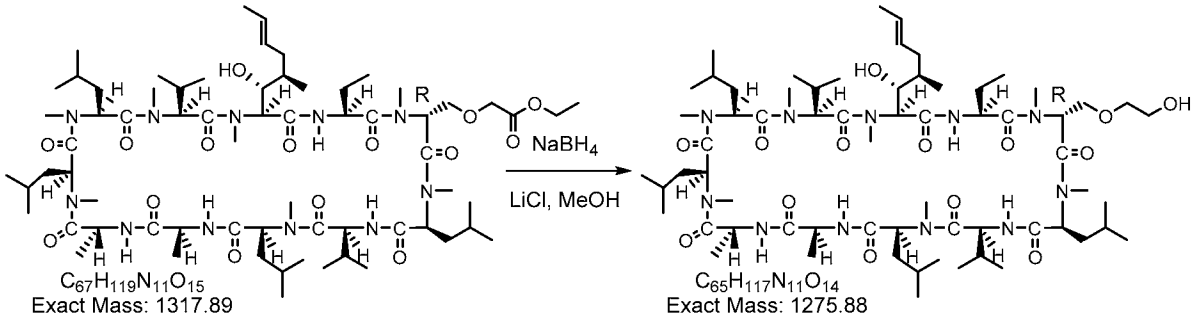


[0178] To a solution of [(R)-(carboxymethoxy)methyl-Sar]-3-cyclosporin (30 mg, 0.02 mmol) in methanol (1 ml) was added a solution of sodium hydroxide (1.00 mg, 0.02 mmol) in water (0.5 ml). The mixture was stirred at room temperature 1 hour and dried in high vacuum to give 28 mg of product [Molecular Formula: $C_{65}H_{114}N_{11}NaO_{15}$; Exact Mass: 1311.84; MS (m/z): 1290.56 $(M+1-Na)^+$; HPLC RT: 10.98 min (C8 reverse phase column:

250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 13

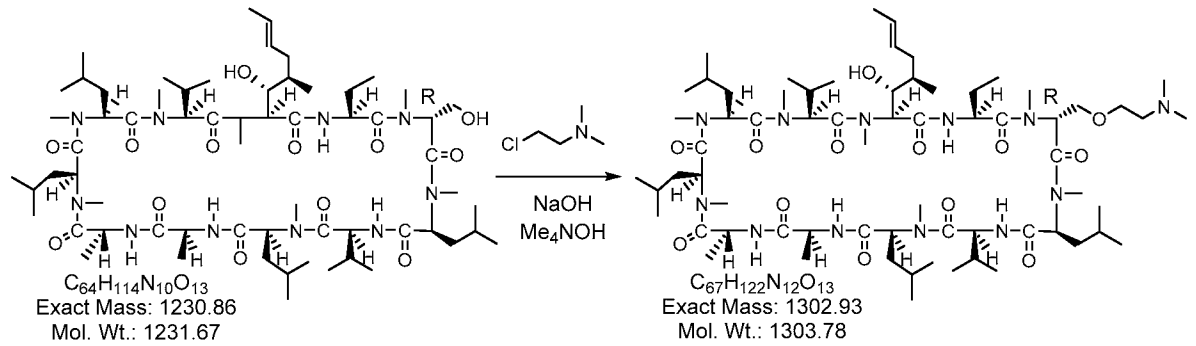
[(R)-(2-Hydroxyethoxy)methyl-Sar]-3-cyclosporin



[0179] To a solution of [(R)-(ethoxycarbonylmethoxy)methyl-Sar]-3-cyclosporin (0.25 g, 0.19 mmol) in methanol (30 ml) were added lithium chloride (0.33 g, 7.85 mmol) and sodium borohydride (0.60 g, 15.89 mmol) in portions. After addition, the mixture was stirred at room temperature overnight. Most of solvent was then evaporated under reduced pressure. Ethyl acetate (50 ml) and water (50 ml) were added. The ethyl acetate layer was separated and washed with brine (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified on silica gel column with (dichloromethane/methanol = 95/5) to give the product [Molecular formula: $C_{65}H_{117}N_{11}O_{14}$; Exact Mass: 1275.88; MS (m/z): 1276.55 $(M+1)^+$; TLC Rf: 0.39 (dichloromethane/methanol = 9/1); HPLC RT: 15.31 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 14

[(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-cyclosporin

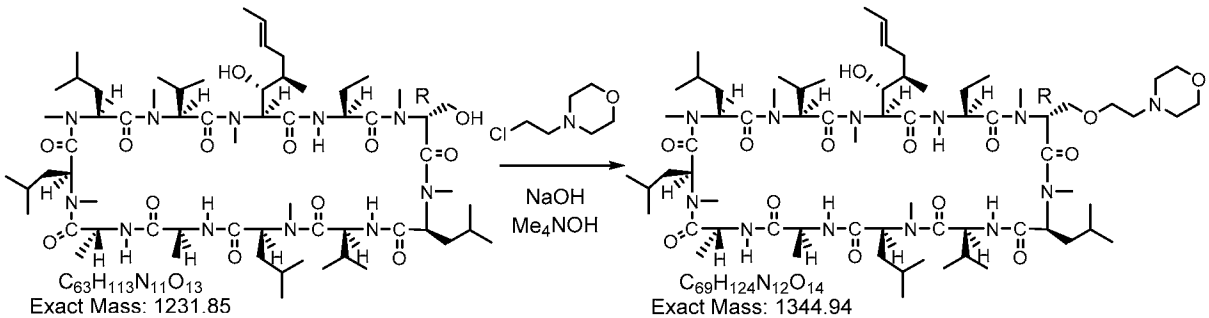


[0180] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (1.03 g, 0.84 mmol) in benzene (50 ml) were added a solution of sodium hydroxide (1.34 g, 33.47 mmol) in

water (1.34 ml), tetramethylammonium hydroxide pentahydrate (3.04 g, 16.73 mmol) and 2-dimethylaminoethyl chloride hydrochloride (2.41 g, 16.73 mmol). The mixture was stirred at room temperature for 5 days. Sodium bicarbonate saturated solution (100 ml) was added and the mixture was separated. Then the aqueous layer was extracted with ethyl acetate (50 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 303 mg of product was obtained [Molecular Formula: $C_{67}H_{122}N_{12}O_{13}$; Exact Mass: 1302.93; MS (m/z): 1303.70 $(M+1)^+$, 1325.85 $(M+Na)^+$; TLC R_f: 0.36 (dichloromethane/methanol = 9/1); HPLC RT: 18.19 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 15

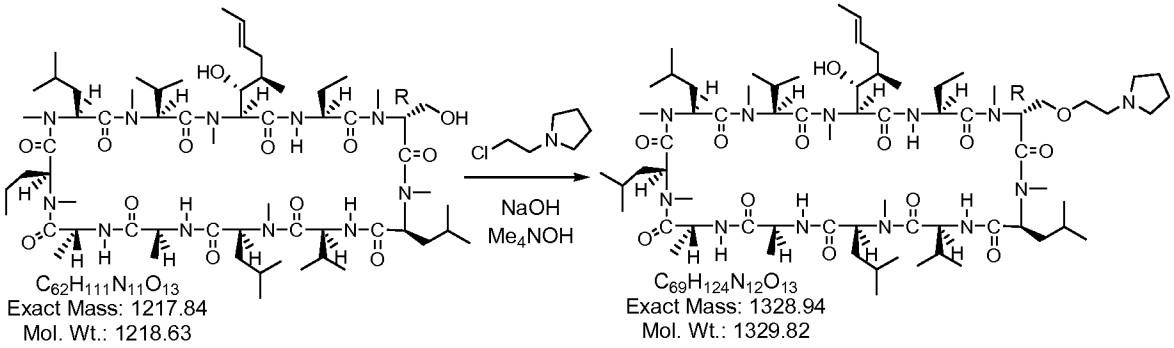
[(R)-(2-(N-Morpholino)ethoxy)methyl-Sar]-3-cyclosporin



[0181] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (0.27 g, 0.22 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (0.70 g, 17.55 mmol) in water (0.70 ml), tetramethylammonium hydroxide pentahydrate (0.80 g, 4.39 mmol) and 2-(4-morpholinyl)ethyl chloride hydrochloride (0.82 g, 4.39 mmol). The mixture was stirred at 30 to 40°C for a week. Sodium bicarbonate saturated solution (30 ml) was added and then the mixture was separated. The aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 56 mg of product was obtained [Molecular Formula: $C_{69}H_{124}N_{12}O_{14}$; Exact Mass: 1344.94; MS (m/z): LCMS: 1345.72 $(M+1)^+$, 1367.83 $(M+Na)^+$; TLC R_f: 0.50 (dichloromethane/methanol = 9/1); HPLC RT: 16.64 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 16

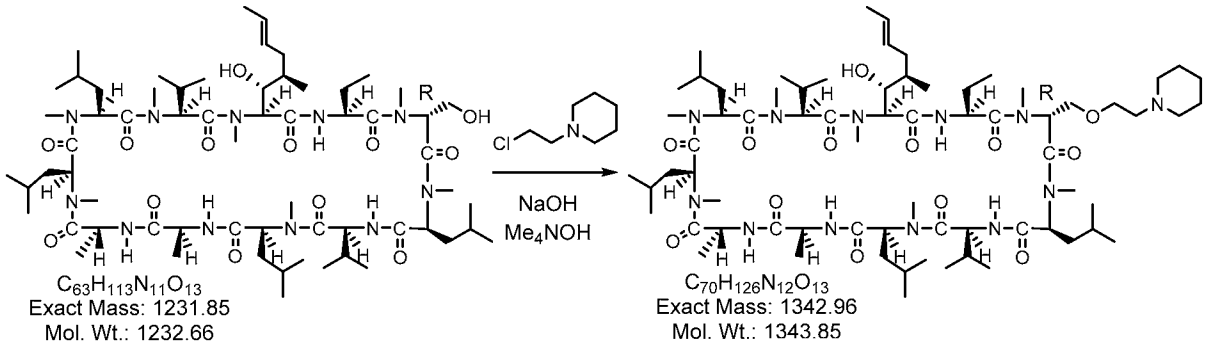
[(R)-(2-(N-Pyrrolidinyl)ethoxy)methyl-Sar]-3-cyclosporin



[0182] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (0.320 g, 0.26 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (0.83 g, 20.80 mmol) in water (0.85 ml), tetramethylammonium hydroxide pentahydrate (0.95 g, 5.20 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (0.88 g, 5.20 mmol). The mixture was stirred at room temperature for a weekend. Sodium bicarbonate saturated solution (30 ml) was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 103 mg of product was obtained [Molecular Formula: $C_{69}H_{124}N_{12}O_{13}$; Exact Mass: 1328.94; MS (m/z): 1329.75 $(M+1)^+$, 1351.82 $(M+Na)^+$; TLC R_f: 0.37 (dichloromethane/methanol = 9/1); HPLC RT: 18.94 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 17

[(R)-(2-(N-Piperidinyl)ethoxy)methyl-Sar]-3-cyclosporin

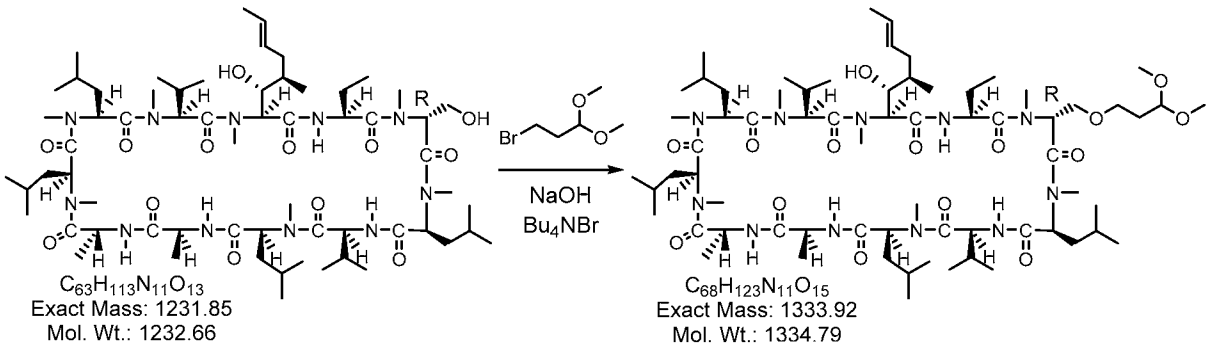


[0183] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (0.28 g, 0.22 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (0.36 g, 9.07 mmol) in water (0.36 ml), tetramethylammonium hydroxide pentahydrate (0.82 mg, 4.53 mmol) and 1-(2-chloroethyl)piperdine hydrochloride (0.83 g, 4.53 mmol). The mixture was stirred at

30 to 40°C for 20 hours. Sodium bicarbonate saturated solution (30 ml) was added and the mixture was separated. Then the aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 121 mg of product was obtained [Molecular Formula: $C_{70}H_{126}N_{12}O_{13}$; Exact Mass: 1342.96; MS (m/z): 1343.76 $(M+1)^+$, 1365.83 $(M+Na)^+$; TLC R_f: 0.44 (dichloromethane/methanol = 9/1); HPLC RT: 19.26 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 18

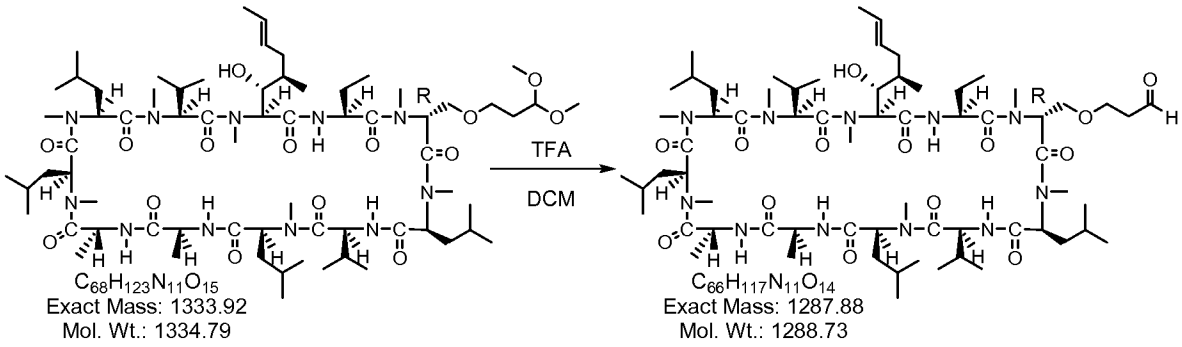
[(R)-(3,3-Dimethoxypropoxy)methyl-Sar]-3-cyclosporin



[0184] To a solution of [(R)-hydroxymethyl-Sar]-3-cyclosporin (0.50 g, 0.41 mmol) in benzene (30 ml) were added a solution of sodium hydroxide (1.00 g, 25.00 mmol) in water (1 ml), 3-bromopropionaldehyde dimethyl acetal (1.80 g, 10.00 mmol) and tetra-n-butylammonium bromide (0.20 g, 0.62 mmol). After stirred at room temperature for 10 hours, the mixture was diluted with ice water and the mixture was separated. The aqueous layer was extracted with dichloromethane (20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 0.48 g of crude product, which was used for next step [Molecular Formula: $C_{68}H_{123}N_{11}O_{15}$; Exact Mass: 1333.92; MS (m/z): 1334.50 $(M+1)^+$].

Example 19

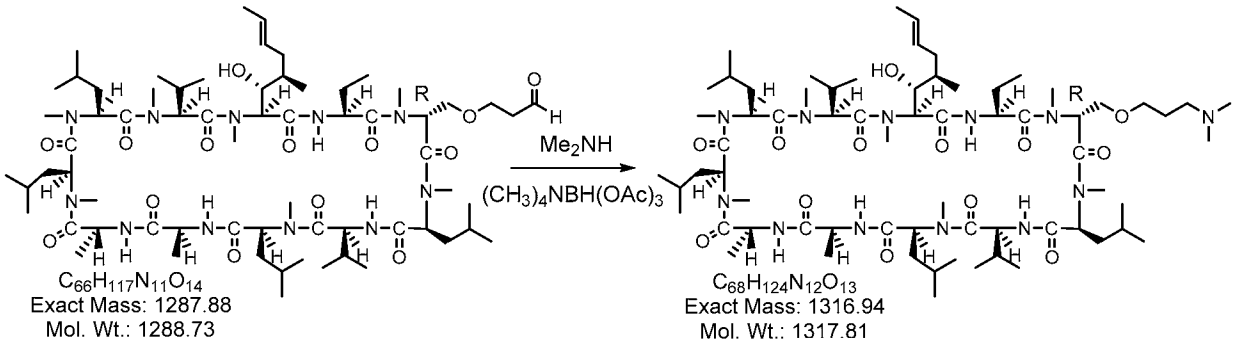
[(R)-(2-Formylethoxy)methyl-Sar]-3-cyclosporin



[0185] To a solution of crude [(R)-(3,3-dimethoxypropoxy)methyl-Sar]-3-cyclosporin (0.48 g, 0.36 mmol) in dichloromethane (30 ml) were added trifuloroacetic acid (5 ml) and water (4 ml) at 0 °C. Then the mixture was allowed to warm to room temperature and stirred for 3 hours. After the mixture was separated, the dichloromethane layer was washed with saturated sodium bicarbonate solution (20 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone = 2/1) to give 0.31 g of product [Molecular Formula: $C_{66}H_{117}N_{11}O_{14}$; Exact Mass: 1287.88; MS (m/z): 1288.63 $(M+1)^+$].

Example 20

[(R)-(3-(N,N-Dimethylamino)propoxy)methyl-Sar]-3-cyclosporin

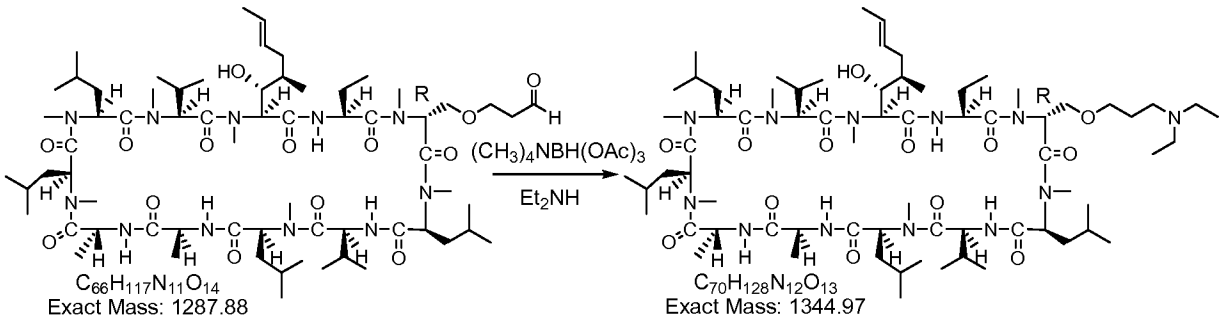


[0186] To a solution of [(R)-(2-formylethoxy)methyl-Sar]-3-cyclosporin (0.13 g, 0.10 mmol) in chloroform (5 ml) were added dimethylamine hydrochloride (0.10 g, 1.22 mmol) and acetic acid (5 drops). After the mixture was stirred at room temperature for 5 minutes, tetramethylammonium triacetoxyborohydride (65 mg, 0.25 mmol) was added in portions and stirring was continued for one hour. Then dichloromethane (10 ml) and saturated sodium bicarbonate solution (10 ml) were added and separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 89

mg of product [Molecular Formula: $C_{68}H_{124}N_{12}O_{13}$; Exact Mass: 1316.94; MS (m/z): 1317.64 $(M+1)^+$; TLC R_f: 0.39 (dichloromethane/methanol = 95/5); HPLC RT: 13.92 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 21

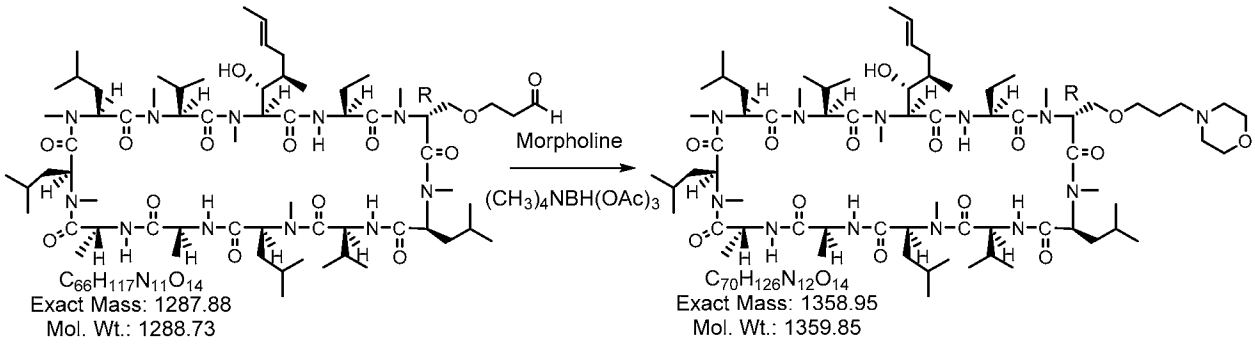
[(R)-(3-(N, N-Diethylamino)propoxy)methyl-Sar]-3-cyclosporin



[0187] To a solution of [(R)-(2-formylethoxy)methyl-Sar]-3-cyclosporin (100 mg, 0.08 mmol) in chloroform (4 ml) were added diethylamine (100 mg, 1.37 mmol) and acetic acid (4 drops). After the mixture was stirred at room temperature for 5 minutes, tetramethylammonium triacetoxyborohydride (50 mg, 0.19 mmol) was added in portions and stirring was continued for 1 hour. Then dichloromethane (10 ml) and saturated sodium bicarbonate solution (10 ml) were added and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 56 mg of product [Molecular Formula: $C_{70}H_{128}N_{12}O_{13}$; Exact Mass: 1344.97; MS (m/z): 1345.71 $(M+1)^+$; TLC R_f: 0.40 (dichloromethane/methanol = 95/5); HPLC RT: 14.59 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 22

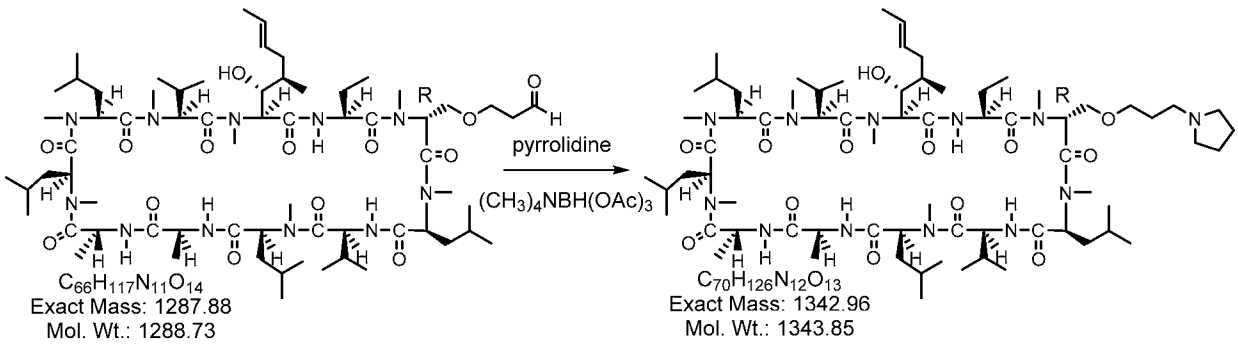
[(R)-(3-(N-Morphlino)propoxy)methyl-Sar]-3-cyclosporin



[0188] To a solution of [(R)-(2-formylethoxy)methyl-Sar]-3-cyclosporin (300 mg, 0.23 mmol) in dichloromethane (15 ml) were added morpholine (101 mg, 1.16 mmol) and tetramethylammonium triacetoxyborohydride (306 mg, 1.16 mmol). The reaction mixture was stirred at room temperature for two hours. Then sodium bicarbonate saturated solution (30 ml) and dichloromethane (15 ml) were added and the mixture was separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 124 mg of product was obtained [Molecular Formula: $C_{70}H_{126}N_{12}O_{14}$; Exact Mass: 1358.95; MS (m/z): 1359.71$(M+1)^+$, 1381.79 $(M+Na)^+$; TLC R_f: 0.40 (dichloromethane/methanol = 9/1); HPLC RT: 14.2 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 23

[(R)-(3-(N-Pyrrolidinyl)propoxy)methyl-Sar]-3-cyclosporin

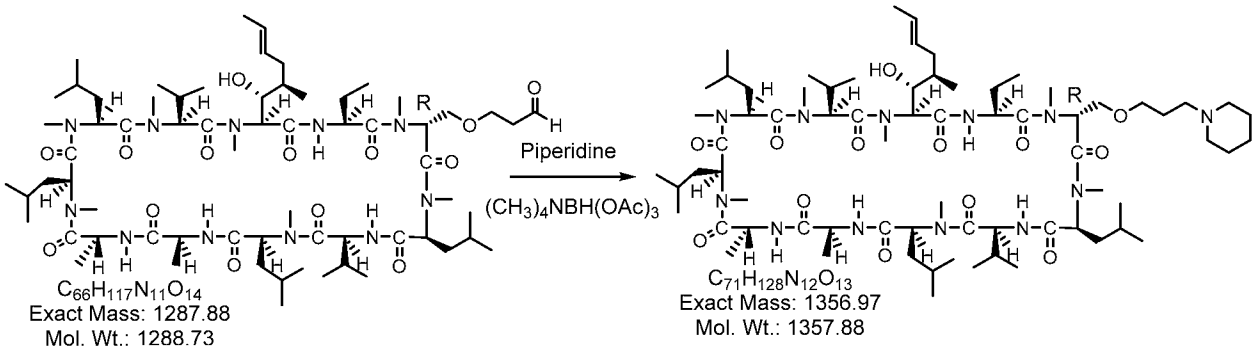


[0189] To a solution of [(R)-α-hydroxymethyl-Sar]-3-cyclosporin (315 mg, 0.24 mmol) in dichloromethane (15 ml) were added pyrrolidine (87 mg, 1.22 mmol) and tetramethylammonium triacetoxyborohydride (322 mg, 1.22 mmol). The reaction mixture was stirred at room temperature for two hours. Then sodium bicarbonate saturated solution (30 ml) and dichloromethane (15 ml) were added and the mixture was separated. The

dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 22 mg of product was obtained [Molecular Formula: $C_{70}H_{126}N_{12}O_{13}$; Exact Mass: 1342.96; MS (m/z): 1343.75 $(M+1)^+$, 1365.82 $(M+Na)^+$; TLC R_f: 0.33 (dichloromethane/methanol = 9/1); HPLC RT: 14.3 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 24

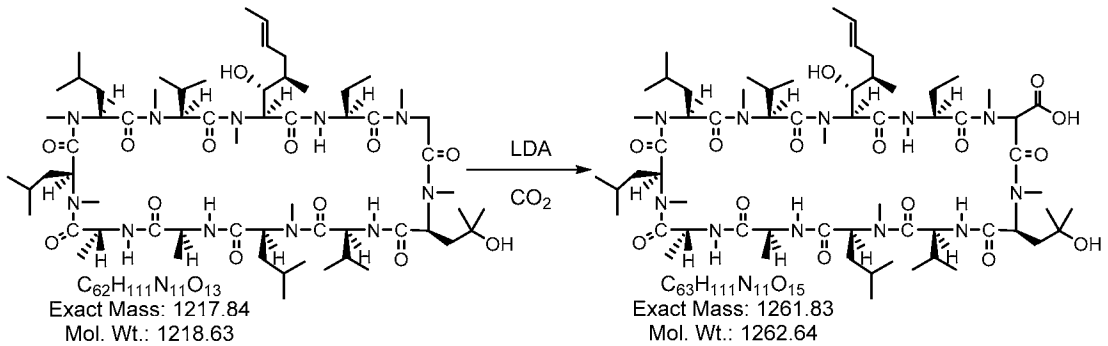
[(R)-(3-(N-Piperidinyl)propoxy)methyl-Sar]-3-cyclosporin



[0190] To a solution of [(R)-(2-formylethoxy)methyl-Sar]-3-cyclosporine (350 mg, 0.27 mmol) in dichloromethane (20 ml) were added piperidine (115 mg, 1.34 mmol) and tetramethylammonium triacetoxyborohydride (352 mg, 1.34 mmol). The reaction mixture was stirred overnight at room temperature. Then sodium bicarbonate saturated solution (30 ml) and dichloromethane (15 ml) were added and the mixture was separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 35 mg of product was obtained [Molecular Formula: $C_{71}H_{128}N_{12}O_{13}$; Exact Mass: 1356.97; MS (m/z): 1357.76 $(M+1)^+$, 1379.83 $(M+Na)^+$; TLC R_f: 0.36 (dichloromethane/methanol = 9/1); HPLC RT: 14.4 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 25

[α-Carboxy-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

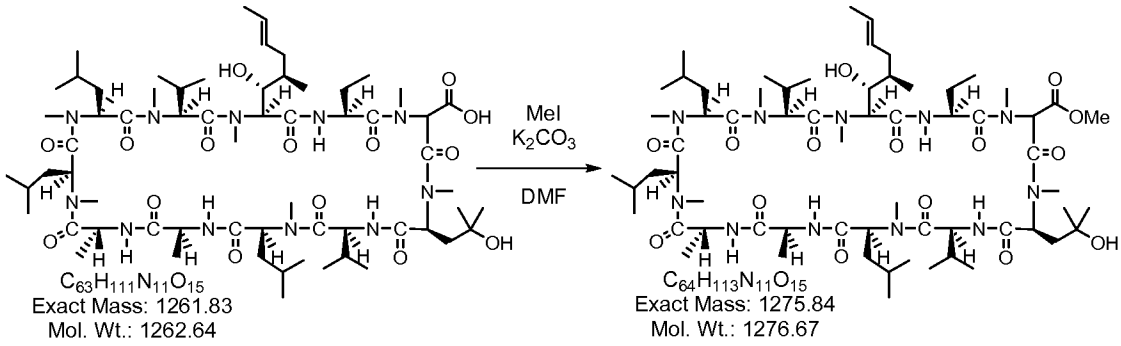


[0191] To a solution of LDA (2.0 M in tetrahydrofuran, 23 ml, 46 mmol) in tetrahydrofuran (80 ml) at –78 °C under nitrogen, [(γ-hydroxy)-N-MeLeu]-4-cyclosporin (4.40 g, 3.61 mmol) in tetrahydrofuran (15 ml) was added over 3 min. After the mixture was stirred at –78 °C for 3 hours, carbon dioxide gas was bubbled into the reaction mixture for 1 hour. Then the mixture was allowed to warm to room temperature slowly and kept stirring for 3 hours. Most of tetrahydrofuran was evaporated. Dichloromethane (100 ml) and water (50 ml) were added. The PH of the mixture was adjusted to around 5 by adding aqueous citric acid solution. The mixture was separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3.20 g of crude product, which was used for next step without purification [Molecular Formula: $C_{63}H_{111}N_{11}O_{15}$; Exact Mass: 1261.83; MS (m/z): 1262.49 $(M+1)^+$].

[0192] [(γ-Hydroxy)-N-MeLeu]-4-cyclosporin was prepared by *Sebekia benihana* biotransformation according to a method described by Kuhnt M. *et al.*, 1996, Microbial Biotransformation Products of Cyclosporin A, *J. Antibiotics*, 49 (8), 781.

Example 26

[α-Methoxycarbonyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

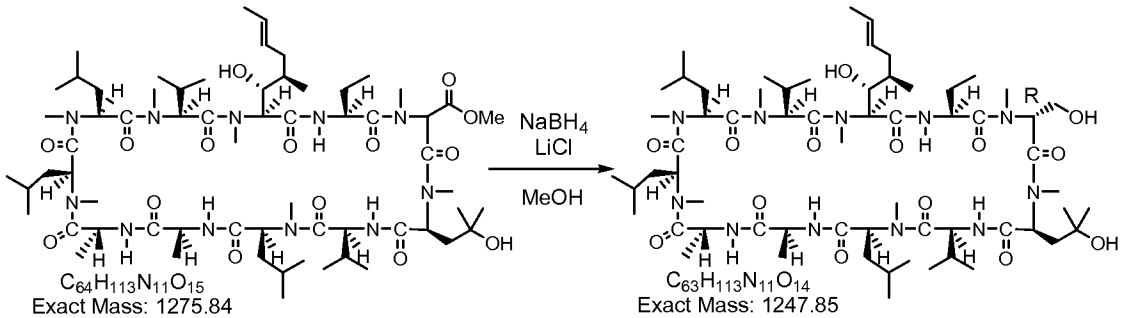


[0193] To a mixture of [α-carboxy-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (3.20 g 2.53 mmol) and potassium carbonate (1.30 g, 9.40 mmol) in N,N-dimethylformamide (20 ml) was added iodomethane (1.80 g, 12.70 mmol). The mixture was stirred overnight at

room temperature. Dichloromethane (80 ml) and water (50 ml) were added and the mixture was separated. The dichloromethane layer was washed with water (25 ml) and brine (25 ml), dried over magnesium sulfate and evaporated under reduced pressure to give crude 3.00 g of product [Molecular Formula: $C_{64}H_{113}N_{11}O_{15}$; Exact Mass: 1275.84; MS (m/z): 1276.75 $(M+1)^+$].

Example 27

[(R)-α-Hydroxymethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

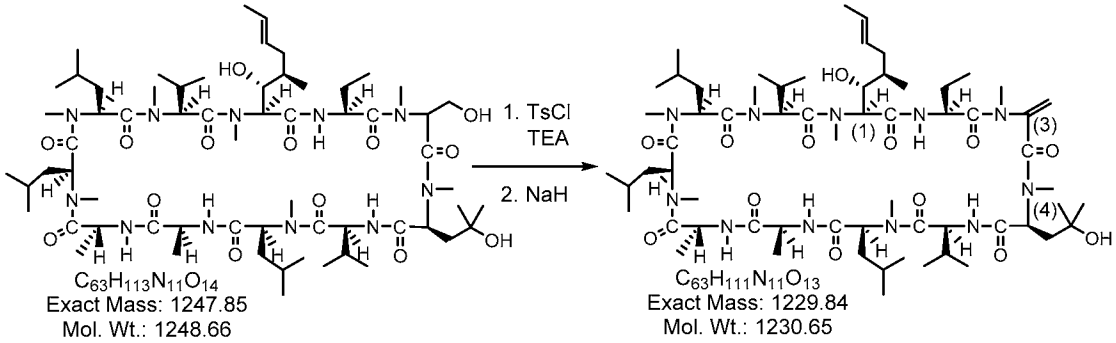


[0194] To a suspension of [α-methoxycarbonyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (3.00 g, 2.35 mmol) and lithium chloride (1.50 g, 35.30 mmol) in methanol (100 ml) was added sodium borohydride (2.50 g, 66.10 mmol) in portions. The mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Dichloromethane (80 ml) and water (50 ml) were added and the mixture was separated. The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 1.30 g of product [Molecular Formula: $C_{63}H_{113}N_{11}O_{14}$; Exact Mass: 1247.85; MS (m/z): 1248.48 $(M+1)^+$; ^1H NMR spectrum (600 MHz, $CDCl_3$, δ in ppm): 0.68 (d, J = 5.4Hz, 3H), 0.80-1.00 (m, 30H), 1.07 (d, J = 6.0Hz, 3H), 1.16 –1.29 (m, 10H), 1.32 (d, J = 7.2Hz, 3H), 1.39-1.46 (m, 2H), 1.59-1.63 (m, 6H), 1.68-1.83 (m, 7H), 2.02-2.11 (m, 4H), 2.31-2.33 (m, 1H), 2.37-2.42 (m, 2H), 2.67 (s, 6H), 3.09 (s, 3H), 3.19 (s, 3H), 3.20 (s, 3H), 3.22 (s, 3H), 3.47 (s, 3H), 3.72-3.75 (m, 1H), 3.82 (br, 1H), 3.97-3.99 (m, 1H), 4.07-4.10 (m, 1H), 4.50-4.52 (m, 1H), 4.65-4.67 (t, J = 8.4 Hz, 1H), 4.79-4.81 (m, 1H), 4.90-4.95 (m, 2H), 5.00 –5.05 (m, 2H), 5.09 (d, J = 10.8Hz, 1H), 5.30-5.35 (m, 2H), 5.46 (d, J = 6.0Hz, 1H), 5.52-5.53 (m, 1H), 5.66-5.68 (m, 1H), 7.12 (d, J = 7.8Hz, 1H), 7.47 (d, J = 8.4Hz, 1H), 7.60 (d, J = 7.2Hz, 1H), 7.87-7.89 (d, J = 9.6Hz, 1H)].

Example 28

[α-Methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

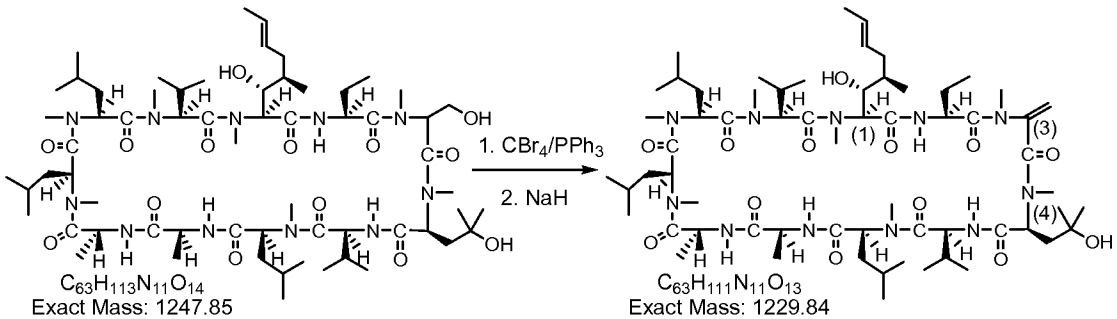
Method 1



[0195] To a solution of [α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (250 mg, 0.20 mmol) in dichloromethane (10 mL) at room temperature were added triethylamine (0.33 mL, d 0.726, 2.40 mmol) and triethylamine hydrochloride (95.6 mg, 1.00 mmol), followed by adding p-toluenesulfonyl chloride (0.23 g, 1.20 mmol) under stirring. The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with brine, dried over magnesium sulfate and the solvent was evaporated under reduced pressure. The reaction mixture of [α-chloromethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular formula: $C_{63}H_{112}ClN_{11}O_{13}$; Exact Mass: 1265.81; MS (m/z): 1266.32 $(M+1)^+$, 1288.43 $(M+Na)^+$] and [α-p-toluenesulfonylmethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular formula: $C_{70}H_{119}N_{11}O_{16}S$; Exact Mass: 1401.856; MS (m/z): 1402.34 $(M+1)^+$, 1424.62 $(M+Na)^+$] was directly used in next step reaction without further purification. To a solution of the above mixture in tetrahydrofuran (20 ml) was added sodium hydride (320 mg, 60% in oil, 8 mmol) at 0 °C. The mixture was stirred at 0 °C for one hour and then warmed up to room temperature for 30 minutes. The reaction was quenched with a saturated ammonia chloride solution. After removing tetrahydrofuran, the crude product was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate/methanol (20/1) to give 45 mg of product (yield: 18 %) [Molecular formula: $C_{63}H_{111}N_{11}O_{13}$; Exact Mass: 1229.84; MS (m/z): 1230.60 $(M+1)^+$, 1252.82 $(M+Na)^+$; TLC R_f: 0.50 (ethyl acetate/methanol = 10/1); HPLC RT: 15.38 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm); ^1H NMR spectrum (600 MHz, $CDCl_3$, δ in ppm): 0.72 (d, J = 5.4Hz, 3H), 0.84-1.00 (m, 30H), 1.17-1.26 (m, 15H), 1.34 (d, J = 6.0 Hz, 3H), 1.44 –1.47 (m, 2H), 1.59-1.62 (m, 6H), 1.69-1.76 (m, 4H),

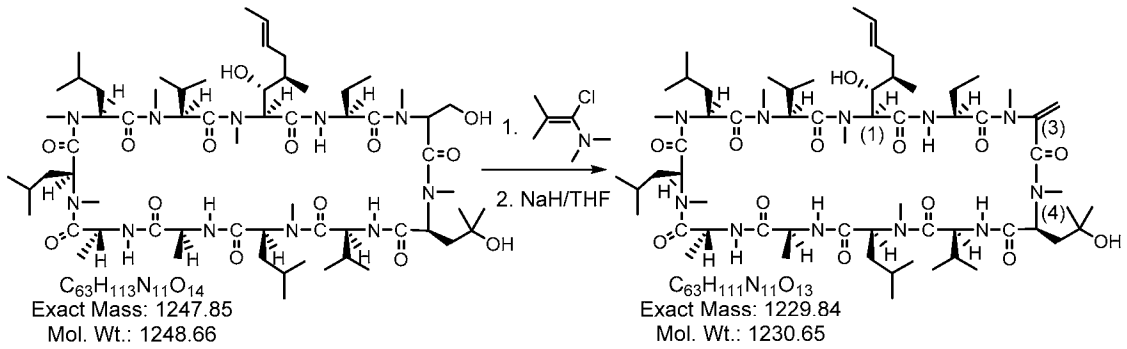
1.94-1.99 (m, 1H), 2.09-2.13 (m, 3H), 2.34-2.37 (m, 3H), 2.65(s, 3H), 2.67 (s, 3H), 3.09 (s, 3H)), 3.10 (s, 3H), 3.19 (s, 3H), 3.44 (s, 3H), 3.46 (s, 3H), 3.80 (m, 1H), 3.91 (m, 1H), 4.47-4.50 (m, 1H), 4.68-4.71(t, J = 9.0Hz, 1H), 4.78-4.81 (m, 1H), 4.98-5.02 (m, 2H), 5.06-5.11 (m, 3H), 5.24 (s, 1H), 5.32 (m, 2H), 5.41-5.43 (m, 2H), 5.64-5.66 (m, 1H), 7.11 (d, J = 7.2Hz, 1H), 7.49 (d, J = 7.2Hz, 1H), 7.74 (d, J = 8.4Hz, 1H), 7.84 (d, J = 9.6Hz, 1H)].

Method 2



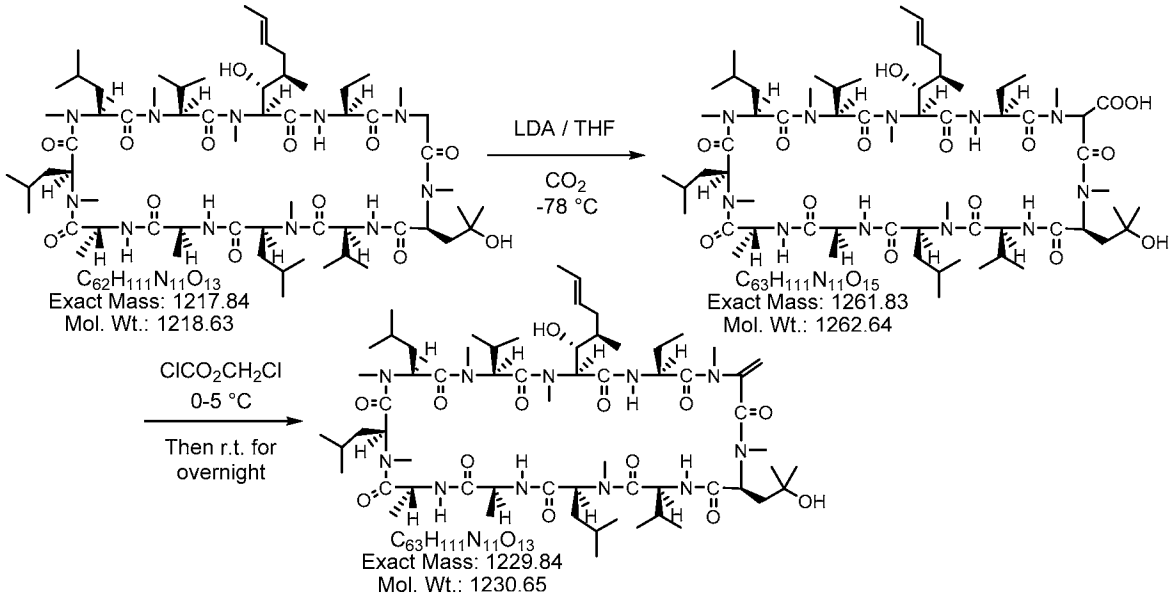
[0196] [(R)-α-Hydroxymethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (crude, 2.00 g), carbon tetrabromide (2.66 g, 8.02 mmol) and triphenylphosphine (2.11 g, 8.02 mmol) were dissolved in dichloromethane (30 ml). The mixture was stirred under nitrogen at room temperature for two hours. Then the mixture was added into a suspension of sodium hydride (60% dispersion in mineral oil) (0.77 g, 19.25 mmol) in tetrahydrofuran (30 ml) under nitrogen at 0 °C. The mixture was stirred at 0 °C for one hour. Most of solvents then were evaporated under reduced pressure. The residue was treated with water (10 ml) slowly at 0 °C. Ethyl acetate (30 ml) and water (30 ml) were added and the mixture was separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone from 90/10 to 70/30) to give 0.68 g product of [α-methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{63}H_{111}N_{11}O_{13}$; Exact Mass: 1229.84; MS (m/z): 1230.50 $(M+1)^+$, 1252.68 $(M+Na)^+$; TLC R_f: 0.50 (ethyl acetate/methanol = 10/1); HPLC RT: 15.36 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Method 3



[0197] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (250 mg, 0.20 mmol) in methylene chloride (10 mL) was added dropwise 1-chloro-N,N,2-trimethyl-1-propenylamine (131 μl, d 1.01, 1.0 mmol) at 0 °C under nitrogen atmosphere. After stirred for 30 minutes at 0 °C, the mixture was allowed to warm to room temperature and stirred for another hour. The reaction mixture was washed with sodium bicarbonate solution, brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude product containing [α-chloromethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular formula: $C_{63}H_{112}ClN_{11}O_{13}$; Exact Mass: 1265.81; MS (m/z): 1266.32 $(M+1)^+$, 1288.43 $(M+Na)^+$] was used in next step reaction without further purification. To a solution of the above crude product in tetrahydrofuran (20 ml) was added sodium hydride (320 mg, 60% in oil, 8 mmol) at 0 °C under stirring. The mixture was stirred at 0 °C for one hour and then warmed up to room temperature for another 30 minutes. The reaction was then quenched with a saturated ammonia chloride solution. After removing tetrahydrofuran, the residue was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate/methanol (20/1) to give 33 mg of product (yield: 13 %) [Molecular formula: $C_{63}H_{111}N_{11}O_{13}$; Exact Mass: 1229.84; MS (m/z): 1230.45$(M+1)^+$, 1252.65 $(M+Na)^+$; TLC R_f: 0.50 (ethyl acetate/methanol = 10/1); HPLC RT: 15.36 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Method 4*

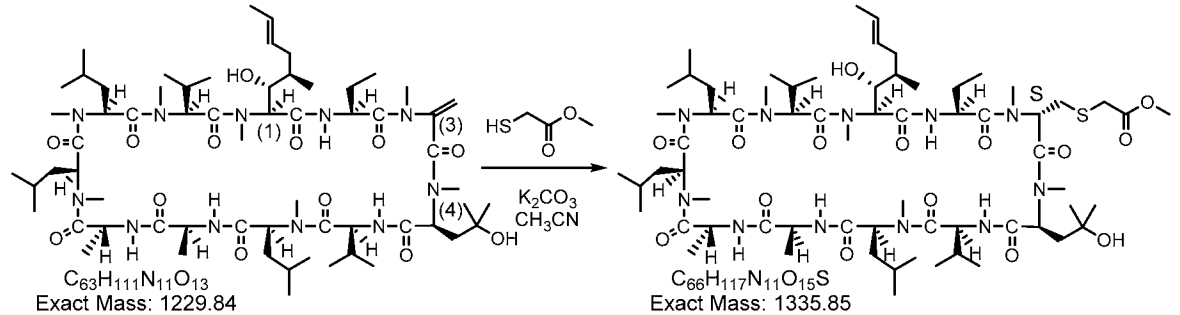


[0198] n-Buli (2.2 M, 49.30 ml, 108.46 mmol) was added into a solution of diisopropylamine (15.39 ml, 108.46 mmol) in tetrahydrofuran (150 ml) at –78 °C under nitrogen. After the reaction mixture was stirred for an hour, a solution of [(γ-hydroxy)-NMeLeu]-4-cyclosporin (12.00 g, 9.86 mmol) in tetrahydrofuran (30 ml) was added over 10 min. The stirring was continued at –78 °C for two hours. Carbon dioxide gas was bubbled through the reaction mixture for two hour and the mixture was stirred at –78 °C for another hour. Then the cooling bath was removed and the reaction mixture was allowed to warm up to room temperature slowly with bubbling out of unreacted carbon dioxide. The mixture was cooled to about 0-5 °C by ice bath and chloromethyl chloroformate (13.98 g, 108.46 mmol) was added. The mixture was allowed to warm to room temperature and stirred for overnight. Water (30 ml) was added to quench the reaction. Most of solvent was then evaporated under reduced pressure. Ethyl acetate (100 ml) and water (80 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography with hexane/acetone (from 90:10 to 70:30) as eluent to give 4.74 g of pure product of [α-Methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{63}H_{111}N_{11}O_{13}$; Exact Mass: 1229.84; MS (m/z): 1230.39 $(M+1)^+$, 152.59 $(M+Na)^+$; TLC R_f: 0.50 (ethyl acetate/methanol = 10/1); HPLC RT: 15.38 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

[0199] *[α-Methylene-Sar]-3-cyclosporin was prepared using a method analogous to the procedure described in WO2012/051194A1.

Example 29

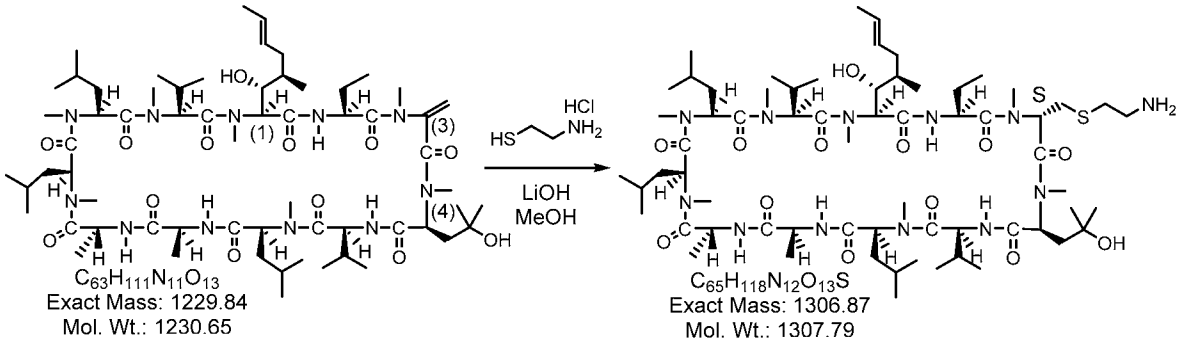
[(S)-(Methoxycarbonylmethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0200] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) and methylmercaptoacetate (0.24 g, 2.00 mmol) were dissolved in acetonitrile (15 ml), followed by adding 20 equivalents of potassium carbonate (0.55 g, 4.0 mmol). The mixture was stirred overnight at room temperature. After removal of solvents, the residue was dissolved in dichloromethane (20 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subject to the flash chromatography using ethyl acetate/methanol as eluent to give product. [Molecular formula: $C_{66}H_{117}N_{11}O_{15}S$; Exact Mass: 1335.84; MS (m/z): 1336.50 $(M+1)^+$, 1358.80 $(M+Na)^+$; TLC R_f: 0.30 (ethyl acetate/methanol = 20/1); HPLC RT: 14.33 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 30

[(S)-(2-Aminoethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

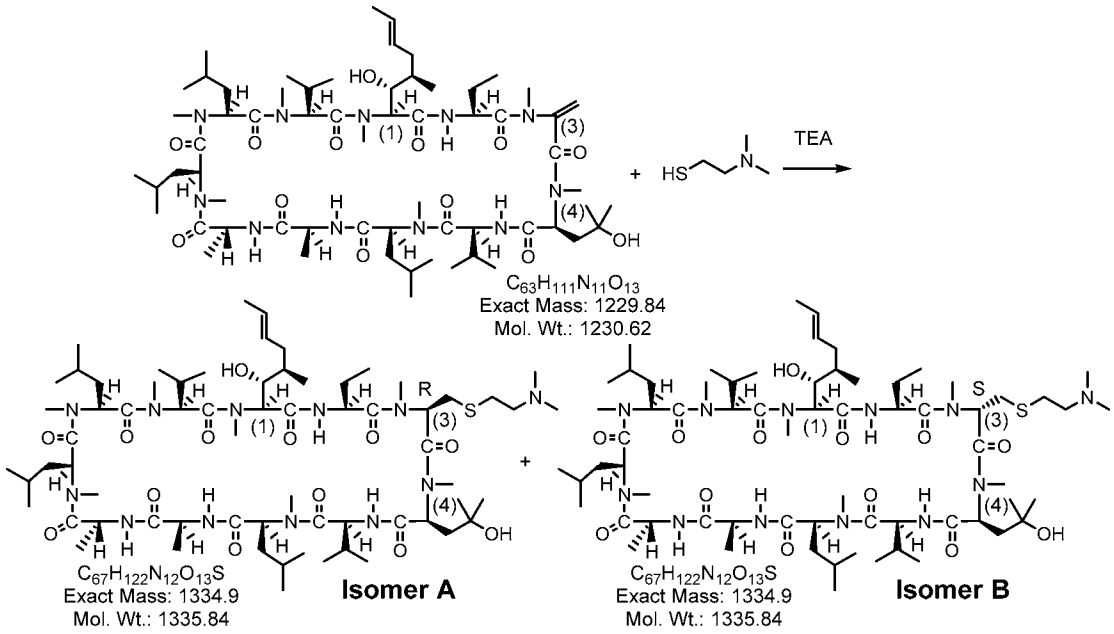


[0201] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.86 g, 0.70 mmol) and 2-aminoethanethiol hydrochloride (0.80 g, 7.00 mmol) were dissolved in

methanol (80 ml), followed by adding 20 equivalents of lithium hydroxide (0.17 g, 7.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was subjected to the flash chromatography using dichloromethane/methanol as eluent to give 0.60 g of product [Molecular Formula: $C_{65}H_{118}N_{12}O_{13}S$; Exact Mass: 1306.87; MS (m/z): 1307.56$(M+1)^+$, 1329.73 $(M+Na)^+$, TLC R_f: 0.025 (dichloromethane/methanol = 5/1); HPLC RT: 10.97 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 31

[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Isomer B) and [(R)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Isomer A)

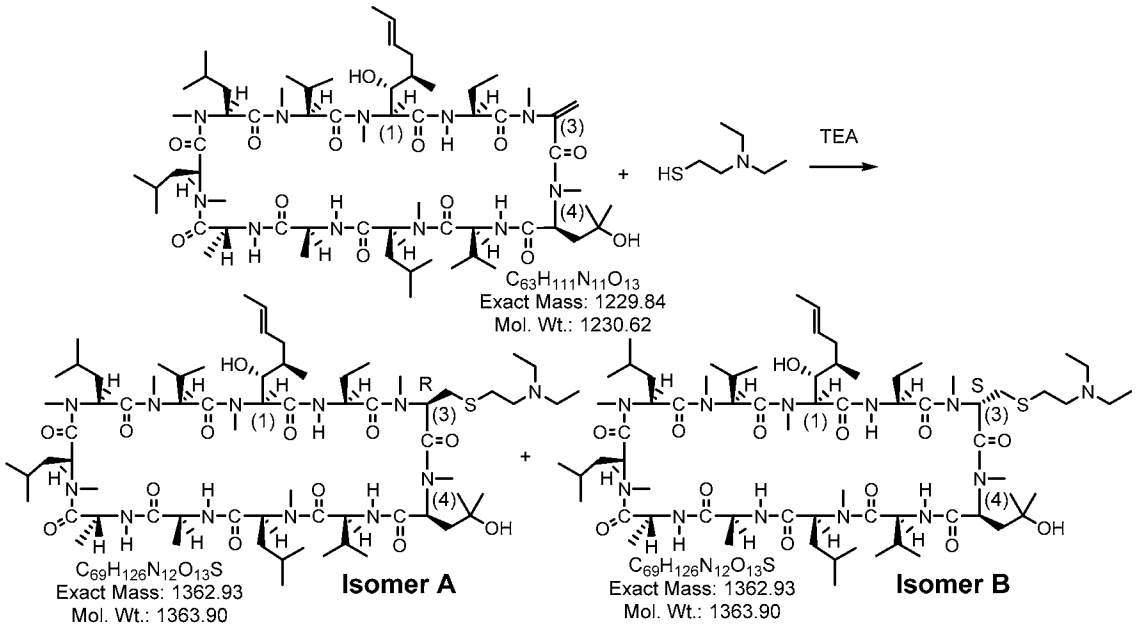


[0202] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.62 g, 0.50 mmol) and 2-(dimethylamino)ethanethiol (0.49 g, 6.00 mmol) were dissolved in methanol (30 ml) followed by adding triethylamine (0.82 ml, 6.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was subjected to chromatography using dichloromethane/methanol as eluent to yield 0.41 g of [(R)-(2-(N,N-dimethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (isomer A) and 0.18 g of [(S)-(2-(N,N-dimethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (isomer B) [Molecular Formula: $C_{67}H_{122}N_{12}O_{13}S$; Exact Mass: 1334.9; MS (m/z): 1335.7$(M+1)^+$; TLC R_f: 0.05 (ethyl acetate/methanol = 5/1); HPLC RT:

10.88 min (isomer A) and 11.30 min (isomer B) (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 32

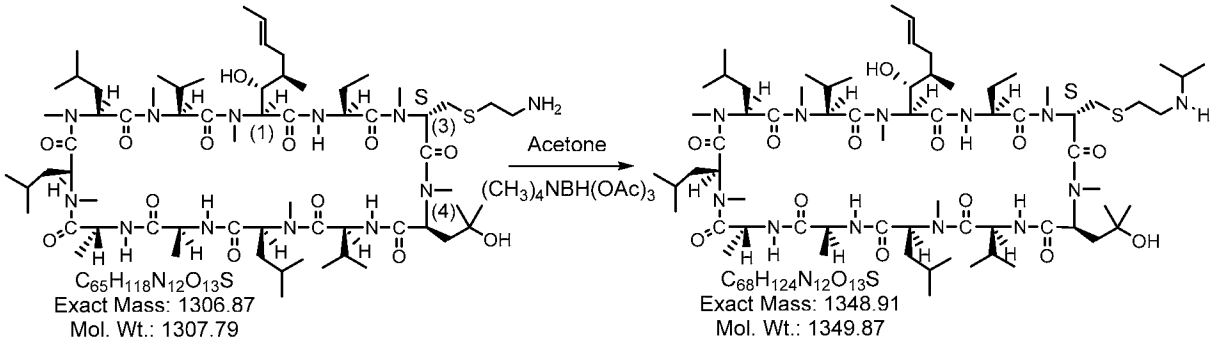
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Isomer B) and [(R)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Isomer A)



[0203] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.31 g, 0.25 mmol) and 2-diethylaminoethanethiol (0.40 g, 3.00 mmol) were dissolved in methanol (30 ml), followed by adding triethylamine (0.41 ml, 3.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was subjected to chromatography using dichloromethane/methanol as eluent to yield 0.15 g of [(R)-(2-(N,N-diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy-N-MeLeu]-4-cyclosporin (isomer A) and 0.10 g of [(S)-(2-(N,N-diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy-N-MeLeu]-4-cyclosporin (isomer B) [Molecular Formula: $C_{69}H_{126}N_{12}O_{13}S$; Exact Mass: 1362.93; MS (m/z): 1363.75 $(M+1)^+$; TLC R_f: 0.1 (ethyl acetate/methanol = 5/1); HPLC RT: 11.64 min (isomer A) and 11.85 min (isomer B) (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 33

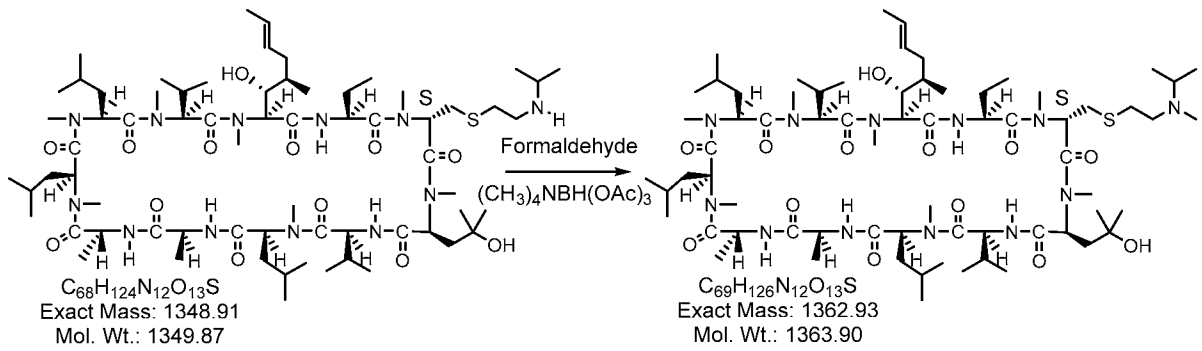
[(S)-(2-(N-Isopropylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0204] [(S)-(2-(Amino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.31 g, 0.25 mmol) and acetone (0.40 ml, 5.44 mmol) were dissolved in chloroform (30 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (164 mg, 0.63mmol) in portions and a few drops of acetic acid. The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using methylene/methanol as eluent to give 0.25 g of pure product [Molecular Formula: $C_{68}H_{124}N_{12}O_{13}S$; Exact Mass: 1348.91; MS (m/z): 1349.59 $(M+1)^+$; TLC R_f: 0.1 (ethyl acetate/methanol = 5/1); HPLC RT: 11.97 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 34

[(S)-(2-(N-Isopropyl-N-methylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

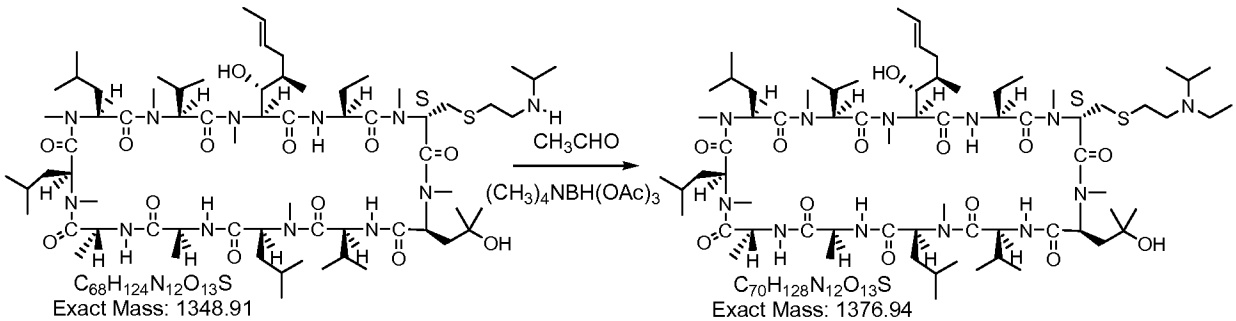


[0205] [(S)-(2-(N-Isopropylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (49 mg, 0.034 mmol) and formaldehyde (100 μl, 37% in water) were mixed

with chloroform (10 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (22 mg, 0.085 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 30 mg of pure product [Molecular Formula: $C_{69}H_{126}N_{12}O_{13}S$; Exact Mass: 1362.93; MS (m/z): 1363.72$(M+1)^+$, 1385.81$(M+Na)^+$; TLC R_f: 0.15 (ethyl acetate/methanol = 5:1); HPLC RT: 12.26 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 35

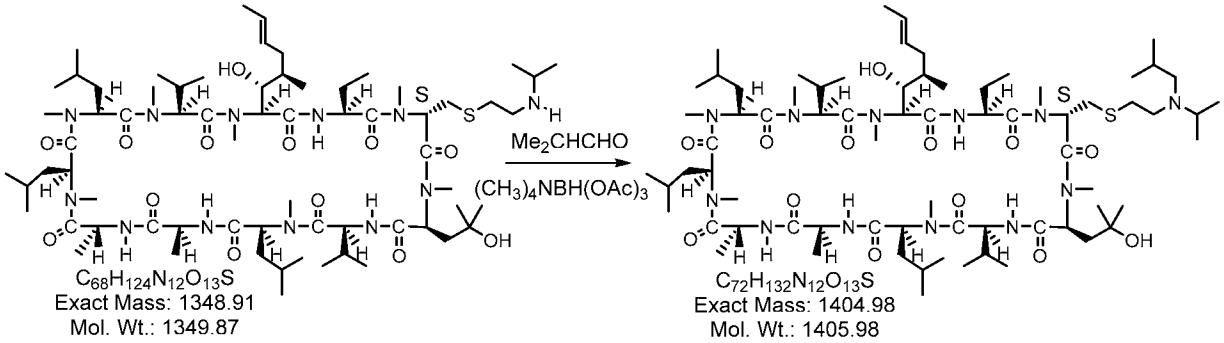
[(S)-(2-(N-Ethyl-N-isopropylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0206] [(S)-(2-(N-Isopropylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (49 mg, 0.034 mmol) and acetaldehyde (100 µl, 37% in water) were mixed with chloroform (10 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (22 mg, 0.085 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 37 mg of pure product [Molecular Formula: $C_{70}H_{128}N_{12}O_{13}S$; Exact Mass: 1376.94; MS (m/z): 1377.84 $(M+1)^+$; TLC R_f: 0.15 (ethyl acetate/methanol = 5/1); HPLC RT: 12.36 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 36

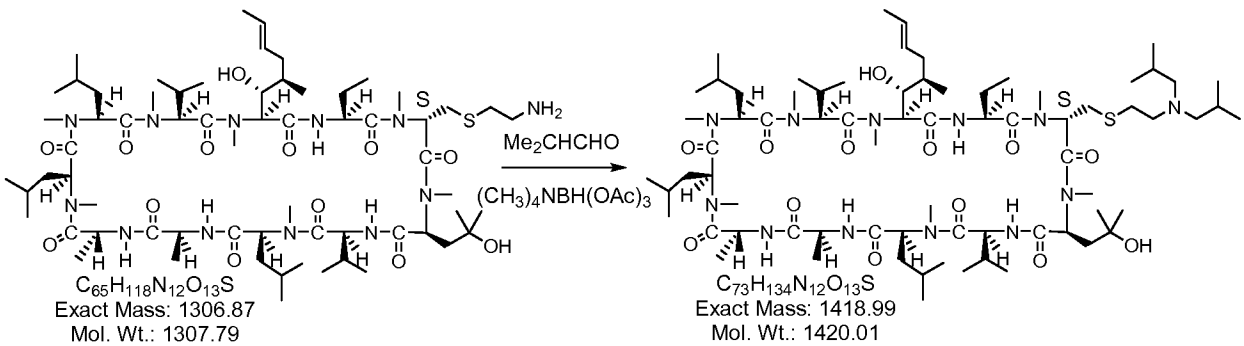
[(S)-(2-(N-Isobutylamino-N-isopropyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0207] [(S)-(2-(N-isopropylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) and isobutyraldehyde (91 μl, 10 mmol) were dissolved in chloroform (30 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (0.13 g, 0.50 mmol) in portion. The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 19 mg of pure product [Molecular Formula: $C_{72}H_{132}N_{12}O_{13}S$; Exact Mass: 1404.98; MS (m/z): 1405.89 $(M+1)^+$, 1427.94 $(M+Na)^+$; TLC R_f: 0.25 (ethyl acetate/methanol = 5/1); HPLC RT: 14.46 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 37

[(S)-(2-(N,N-Diisobutylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

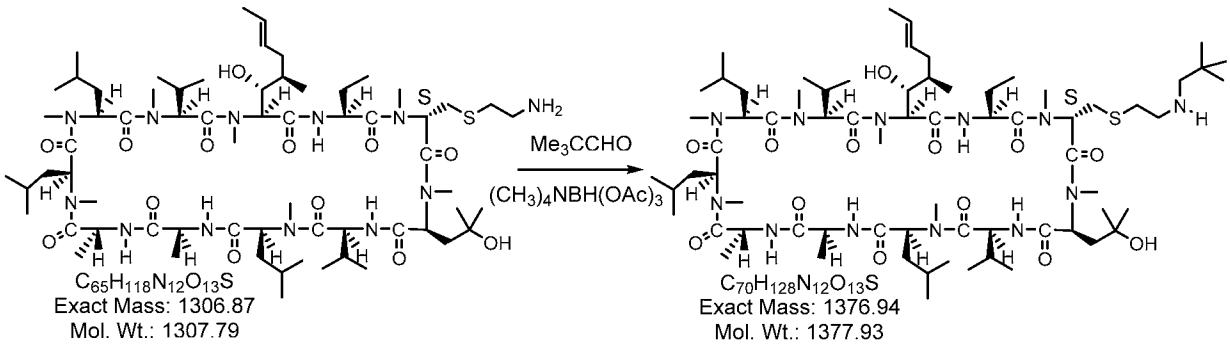


[0208] [(S)-(2-Aminoethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (42 mg, 0.032 mmol) and isobutyraldehyde (15 μl, 0.165 mmol) were dissolved in

chloroform (10 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (21 mg, 0.080 mmol)in portions. The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 23 mg of pure product [Molecular Formula: $C_{73}H_{134}N_{12}O_{13}S$; Exact Mass: 1418.99; MS (m/z): 1419.73$(M+1)^+$, 1441.87$(M+Na)^+$; TLC R_f: 0.36 (ethyl acetate/methanol = 5:1); HPLC RT: 14.46 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 38

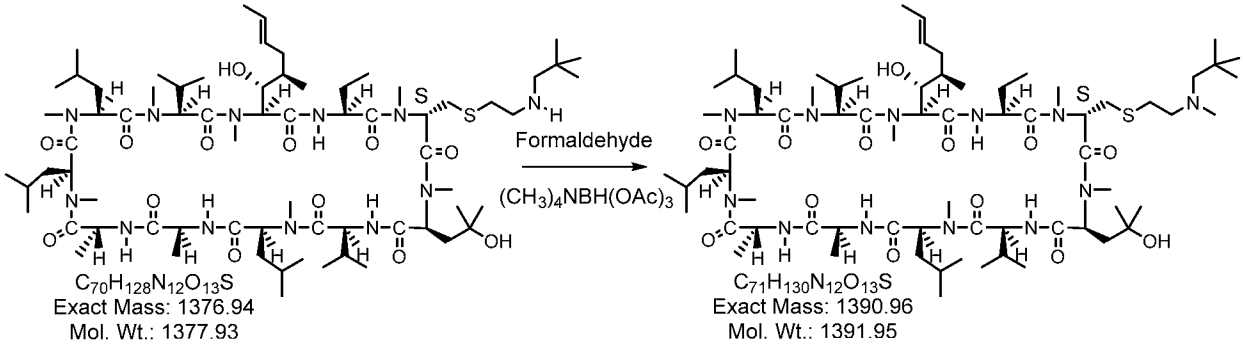
[(S)-(2-(N-Neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0209] [(S)-(2-(Amino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.45 g, 0.34 mmol) and pivalaldehyde (100 µl, 37% in water) were mixed with chloroform (50 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (0.22 g, 0.85 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 11 mg of pure product [Molecular Formula: $C_{70}H_{128}N_{12}O_{13}S$; Exact Mass: 1376.94; MS (m/z): 1377.72 $(M+1)^+$, 1399.82 $(M+Na)^+$; TLC R_f: 0.15 (ethyl acetate/methanol = 5/1); HPLC RT: 12.36 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 39

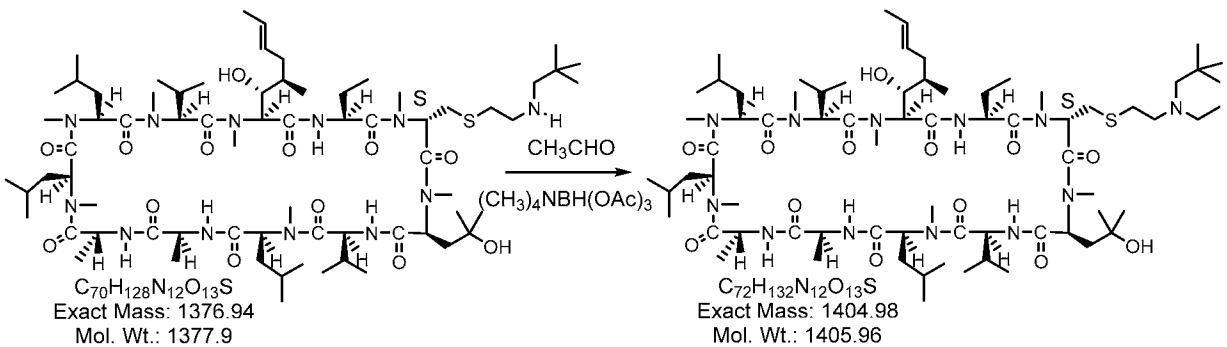
[(S)-(2-(N-Methyl-N-neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0210] [(S)-(2-(N-Neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (49 mg, 0.034 mmol) and formaldehyde (100 µl, 37% in water) were mixed with chloroform (10 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (22 mg, 0.085 mmol. The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 31 mg of pure product [Molecular Formula: $C_{71}H_{130}N_{12}O_{13}S$; Exact Mass: 1390.96; MS (m/z): 1391.71 $(M+1)^+$, 1413.86 $(M+Na)^+$; TLC R_f: 0.25 (ethyl acetate/methanol = 5/1); HPLC RT: 13.28 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 40

[(S)-(2-(N-Ethyl-N-neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

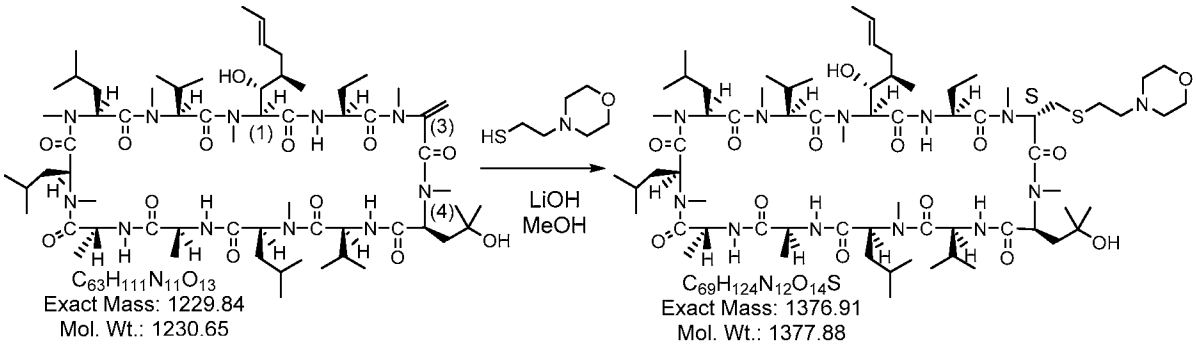


[0211] [(S)-(2-(N-Neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (46 mg, 0.034 mmol) and acetaldehyde (10 µl, 0.17 mmol) were dissolved in

chloroform/methanol, followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (22 mg, 0.085 mmol) in portions. The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 28 mg of product [Molecular Formula: $C_{72}H_{132}N_{12}O_{13}S$; Exact Mass: 1404.98; MS (m/z): 1405.75 $(M+1)^+$, 1427.95 $(M+Na)^+$; TLC R_f: 0.25 (ethyl acetate/methanol = 5/1); HPLC RT: 13.65 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 41

[(S)-(2-(N-Morpholino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

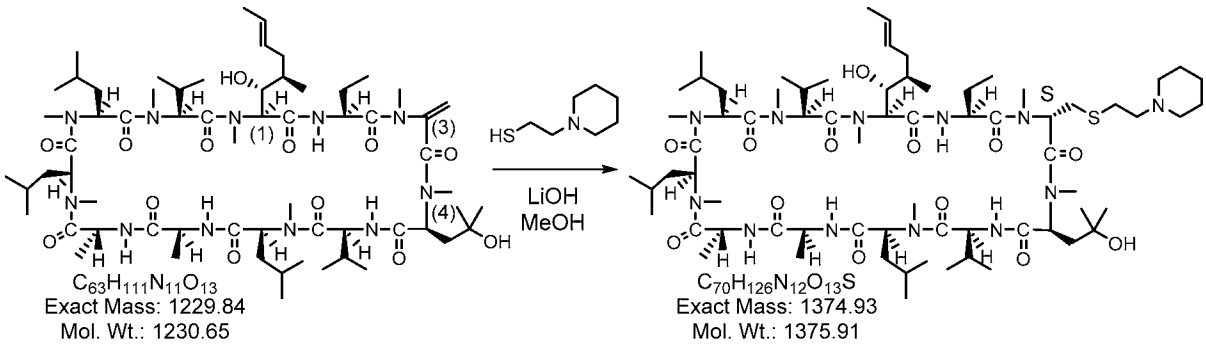


[0212] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (260 mg, 0.21 mmol) and 2-morpholinoethanethiol (300 mg, 2.04 mmol) in methanol (30 ml) was added lithium hydroxide (140 mg, 5.83 mmol). The reaction mixture was stirred at room temperature overnight. Most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give 102 mg of product [Molecular Formula: $C_{69}H_{124}N_{12}O_{14}S$; Exact Mass: 1376.91; MS (m/z): 1399.85 $(M+Na)^+$; TLC Rf: 0.30 (dichloromethane/methanol = 9/1); HPLC RT: 11.03 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm); ^1H NMR spectrum (600 MHz, $CDCl_3$, δ in ppm): 0.68 (d, J=6.6Hz, 3 H), 0.79 (d, J = 6.6Hz, 3H), 0.82 (m, 6H,), 0.85 (d, J = 6.6Hz, 3H), 0.88 (d, J = 7.2Hz, 3H), 0.90 (d, J = 6.6Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.97-1.00 (m, 9 H), 1.08 (d, J=6.6Hz, 3H),

1.21-1.25 (m, 11H), 1.31 (d, J=7.2Hz, 3H), 1.39-1.47 (m, 2 H), 1.54-1.61 (m, 8H), 1.66-1.70 (m, 2 H), 1.75 (m, 1H), 2.01-2.11 (m, 4 H), 2.36-2.43 (m, 7H), 2.55-2.59 (m, 2 H), 2.67 (m, 8 H), 2.93-3.04 (m, 2H), 3.10 (s, 3 H), 3.24 (s, 6H), 3.26 (s, 3H), 3.48 (s, 3H), 3.52 (br, 1H), 3.67 (m, 6H), 4.51 (m, 1 H), 4.59 (t, J =8.4Hz, 1H), 4.81 (m, 1 H), 4.94-5.00 (m, 2H), 5.04 (t, J=6.6Hz, 1H), 5.08 (d, J=10.8Hz,1H), 5.27-5.31 (m, 1H), 5.33-5.37 (m, 1H),5.48 (m, 2H), 5.67 (m,1H), 7.14 (d, J=7.8Hz, 1H), 7.49 (d, J=7.8Hz, 1H), 7.64 (d, J=8.4Hz, 1H), 8.11 (d, J=9.6Hz, 1H)].

Example 42

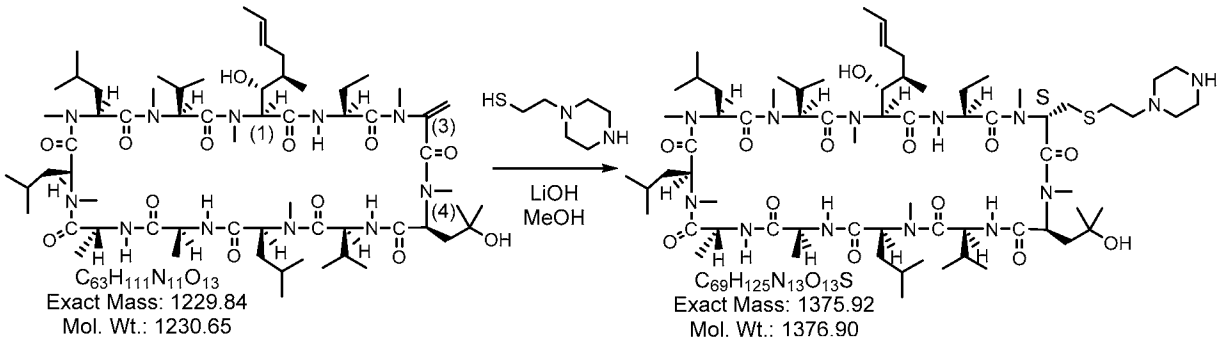
[(S)-(2-(N-Piperidinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0213] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.37 g, 0.30 mmol) and 2-(N-piperidino)ethylthiol (0.44 g, 3.00 mmol) were dissolved in methanol (30 ml), followed by adding 10 equivalents of lithium hydroxide. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.20 g of product [Molecular Formula: $C_{70}H_{126}N_{12}O_{13}S$; Exact Mass: 1374.93; MS (m/z): 1375.65 $(M+1)^+$, 1397.80 $(M+Na)^+$; TLC R_f: 0.18 (ethyl acetate/methanol = 5/1); HPLC RT: 12.09 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 43

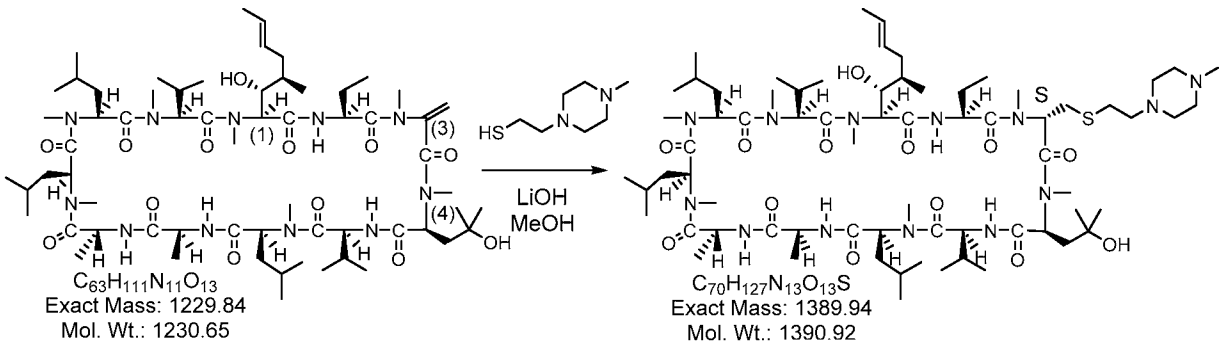
[(S)-2-(N-Piperazinylethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0214] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (1.37 g, 1.11 mmol) and 2-mercaptoethylpiperazine (0.49 g, 3.33 mmol) were dissolved in methanol (25 ml), followed by adding lithium hydroxide (0.26 g, 11.10 mmol). The mixture was stirred at room temperature overnight. Most of solvent was evaporated under reduced pressure. The residue was mixed with ethyl acetate (60 ml) and saturated sodium bicarbonate solution (60 ml) and separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{69}H_{125}N_{13}O_{13}S$; Exact Mass: 1375.92; MS (m/z): 1376.55 $(M+1)^+$, 1398.69 $(M+Na)^+$; TLC R_f: 0.11 (dichloromethane/methanol = 9:1); HPLC RT: 8.06 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 44

[(S)-(2-(4-Methyl-N-piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

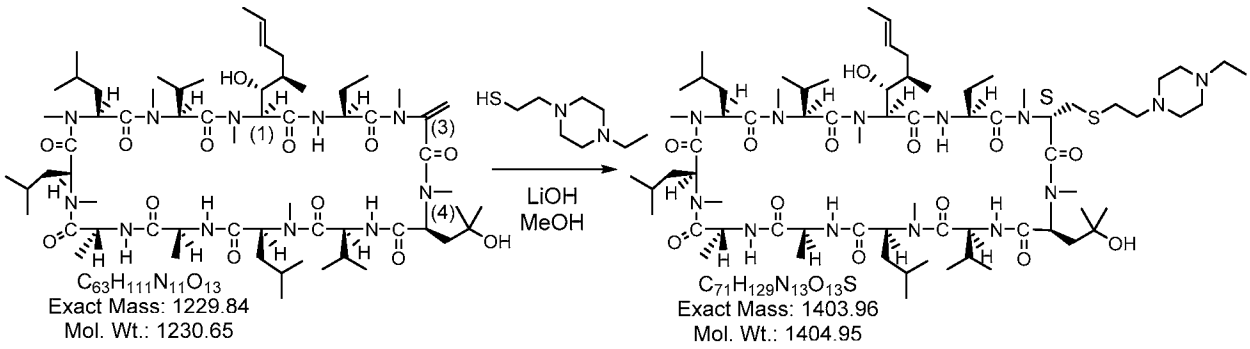


[0215] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.30 g, 0.24 mmol) and 2-(4-methylpiperazino)ethylthiol (0.42 g, 2.62 mmol) were dissolved in methanol (30 ml), followed by adding 10 equivalents of lithium hydroxide. The mixture

was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in methylene chloride (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.22 g of product [Molecular Formula: $C_{70}H_{127}N_{13}O_{13}S$; Exact Mass: 1389.94; MS (m/z): 1390.9 $(M+1)^+$; TLC R_f: 0.08 (ethyl acetate/methanol = 5/1); HPLC RT: 10.07 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 45

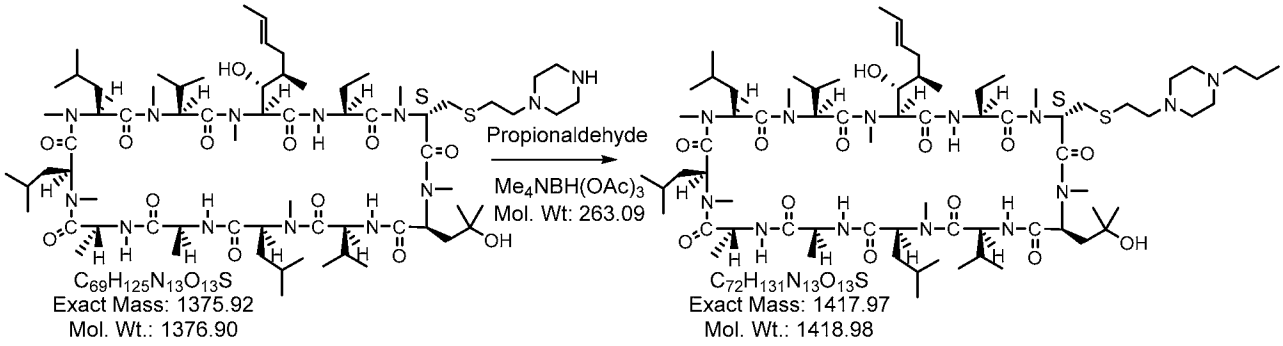
[(S)-(2-(4-Ethyl-N-piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0216] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.30 g, 0.24 mmol) and 3-(1-ethyl-4-piperazino)ethylthiol (0.30 g, 1.72 mmol) were dissolved in methanol (15 ml), followed by adding lithium hydroxide (58 mg, 2.41 mmol). The mixture was stirred overnight at room temperature. Then most of the solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 94/6) to give product [Molecular formula: $C_{71}H_{129}N_{13}O_{13}S$; Exact Mass: 1403.96; MS (m/z): 1404.55 $(M+1)^+$; TLC Rf: 0.30 (dichloromethane/methanol = 85/15); HPLC RT: 8.83 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 46

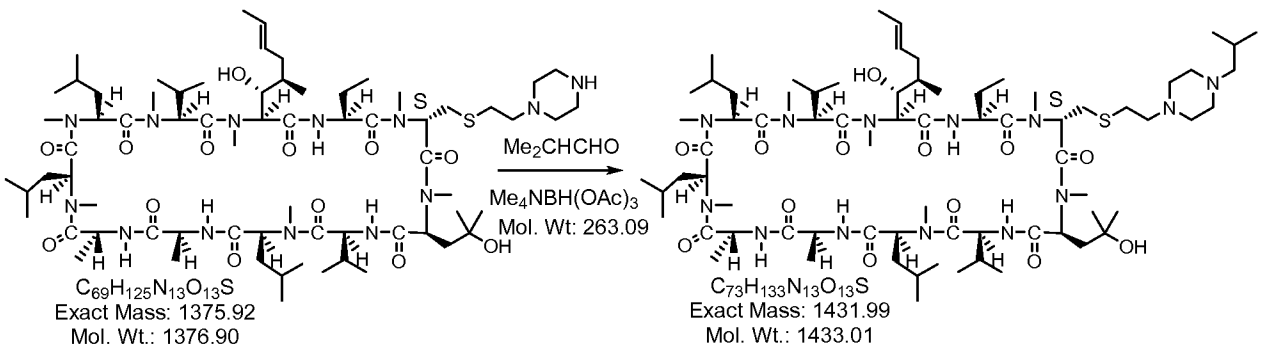
[(S)-2-(4-Propyl-N-piperazinylethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0217] [(S)-(2-(N-Piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (80 mg, 0.058 mmol) and propionaldehyde (MW 58.08, d 0.81, 42 µl, 0.580 mmol) were dissolved in dichloromethane (25 ml), followed by adding tetramethylammonium triacetoxyborohydride (153 mg, 0.580 mmol) in portions and acetic acid (3 drops). The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and methanol as eluent to give product [Molecular Formula: $C_{72}H_{131}N_{13}O_{13}S$; Exact Mass: 1417.97; MS (m/z): 1418.60 $(M+1)^+$, 1440.79 $(M+Na)^+$; TLC R_f: 0.37 (dichloromethane/methanol = 9:1); HPLC RT: 9.61 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 47

[(S)-(2-(4-Isobutyl-N-piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

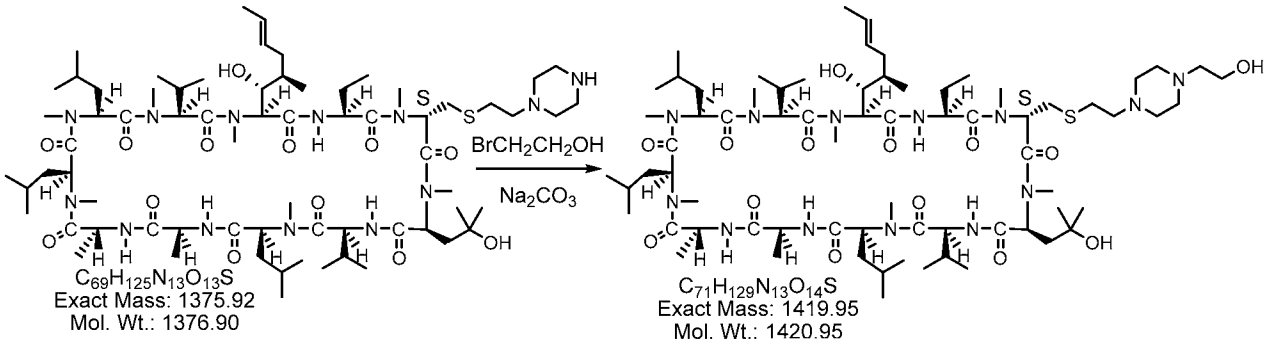


[0218] [(S)-(2-(N-piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (80 mg, 0.058 mmol) and isobutyraldehyde (MW 72.11, d 0.794, 53 µl, 0.58

mmol) were dissolved in dichloromethane (25 ml), followed by adding tetramethylammonium triacetoxyborohydride (153 mg, 0.58 mmol) in portions and acetic acid (3 drops). The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and methanol as eluent to give product [Molecular Formula: $C_{73}H_{133}N_{13}O_{13}S$; Exact Mass: 1431.99; MS (m/z): 1432.63 $(M+1)^+$, 1454.78 $(M+Na)^+$; TLC R_f: 0.44 (dichloromethane/methanol = 9:1); HPLC RT: 10.08 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 48

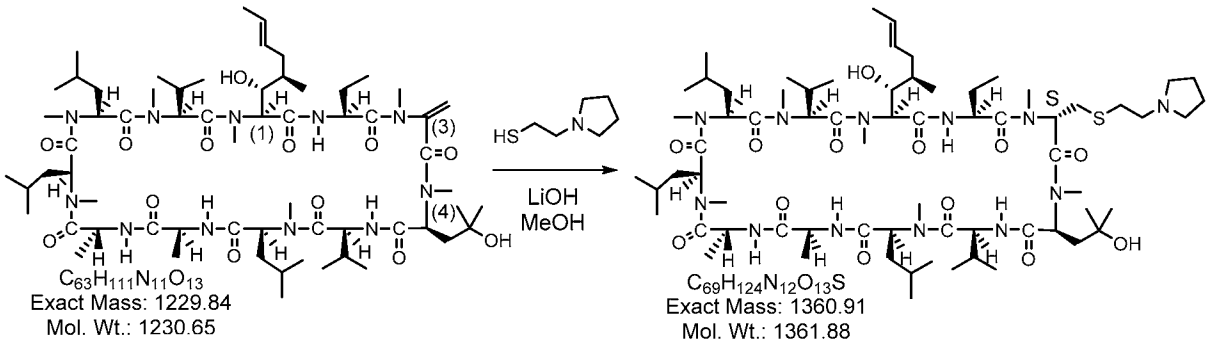
[(S)-(2-(4-(2-Hydroxyethyl)-N-piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0219] [(S)-(2-(N-Piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (80 mg, 0.058 mmol) and 2-bromoethanol (FW 124.97 , d 1.762, 41 μl, 0.58 mmol) were dissolved in dichloromethane (15 ml), followed by adding sodium carbonate (15.4 mg, 0.15 mmol). The mixture was stirred at room temperature for a weekend. Then the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and methanol as eluent to give 20.8 mg of product [Molecular Formula: $C_{71}H_{129}N_{13}O_{14}S$; Exact Mass: 1419.95; MS (m/z): 1420.52 $(M+1)^+$, 1442.72 $(M+Na)^+$; TLC R_f: 0.20 (dichloromethane/methanol = 9:1); HPLC RT: 8.79 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 49

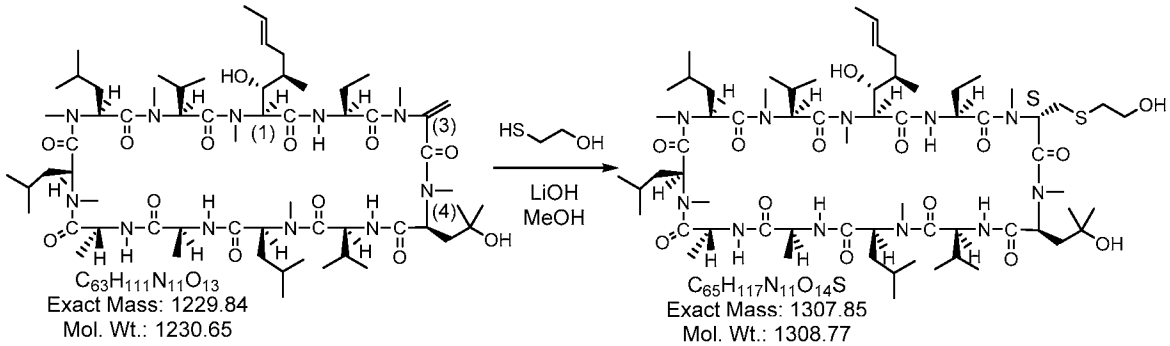
[(S)-(2-(N-Pyrrolidinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0220] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (280 mg, 0.23 mmol) and 2-(N-pyrrolidinyl)ethanethiol (280 mg, 2.14 mmol) in methanol (30 ml) was added lithium hydroxide (114 mg, 4.75 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 126 mg of product [Molecular Formula: $C_{69}H_{124}N_{12}O_{13}S$; Exact Mass: 1360.91; MS (m/z): 1361.80 $(M+1)^+$; TLC R_f: 0.23 (dichloromethane/methanol = 95/5); HPLC RT: 11.59 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 50

[(S)-(2-Hydroxylethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

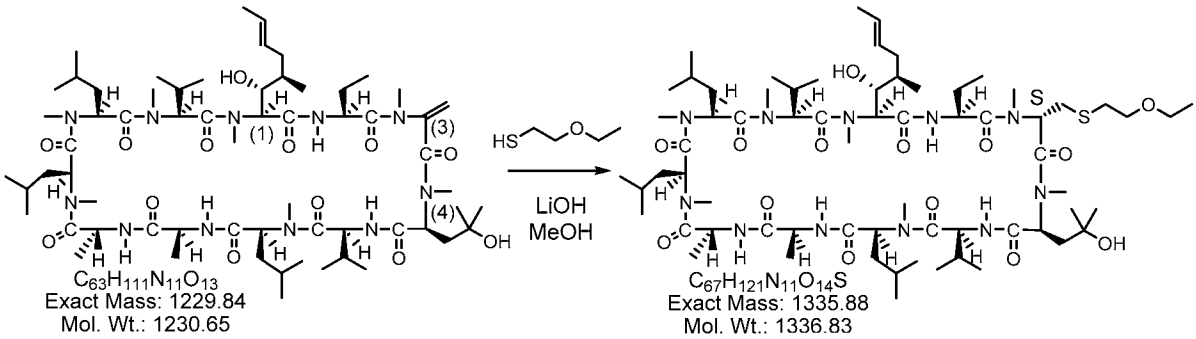


[0221] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (200 mg, 0.16 mmol) and 2-mercaptoethanol (MW 78.13, d 1.114, 112 µl, 1.60 mmol) were dissolved in methanol (10 ml), followed by adding lithium hydroxide (23 mg, 0.96 mmol). The mixture was stirred at room temperature overnight. Most of solvent was evaporated under reduced

pressure. The residue was mixed with ethyl acetate (20 ml) and saturated sodium bicarbonate solution (20 ml) and separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{65}H_{117}N_{11}O_{14}S$; Exact Mass: 1307.85; MS (m/z): 1308.44 $(M+1)^+$, 1330.68 $(M+Na)^+$; TLC R_f: 0.41 (dichloromethane/methanol = 9:1); HPLC RT: 12.61 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 51

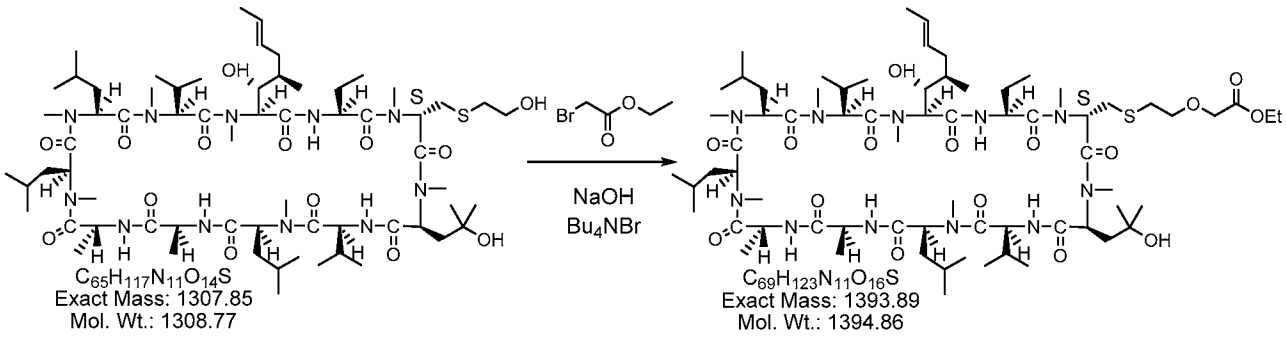
[(S)-2-Ethoxyethylthiomethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.12 mmol) and 2-ethoxyethanethiol (160 mg, 1.51 mmol) in methanol (10 ml) was added lithium hydroxide (50 mg, 2.08 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate/methanol = 97/3) to give a pure product [Molecular formula: $C_{67}H_{121}N_{11}O_{14}S$; Exact Mass: 1335.88; MS (m/z): 1336.49 $(M+1)^+$; TLC Rf: 0.43 (dichloromethane/methanol = 97/3); HPLC RT: 15.51 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 52

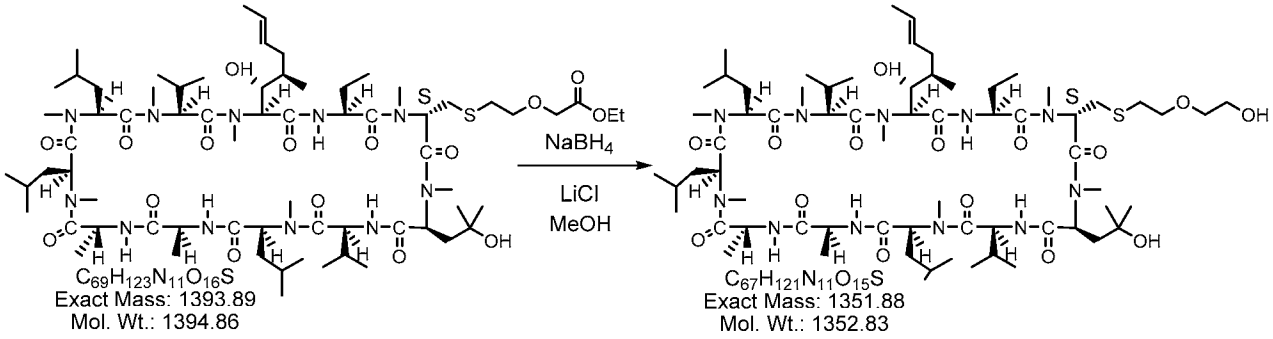
[(S)-(2-(Ethoxycarbonylmethoxy)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



To a solution of [(S)-(2-hydroxyethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.28 g, 0.21 mmol) in benzene (15 ml) were added a solution of sodium hydroxide (0.60 g, 15.00 mmol) in water (1 ml), ethyl bromoacetate (1.50 g, 8.98 mmol) and tetra-n-butylammonium bromide (0.20 g, 0.62 mmol). The mixture was stirred at room temperature for 10 hours. After diluted with ice water, the mixture was separated. The aqueous layer was extracted with dichloromethane (15 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate/methanol = 97/3) to give a pure product [Molecular Formula: $C_{69}H_{123}N_{11}O_{16}S$; Exact Mass: 1393.89; MS (m/z): 1394.48 $(M+1)^+$; TLC R_f: 0.45 (dichloromethane/methanol = 95/5); HPLC RT: 15.28 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 53

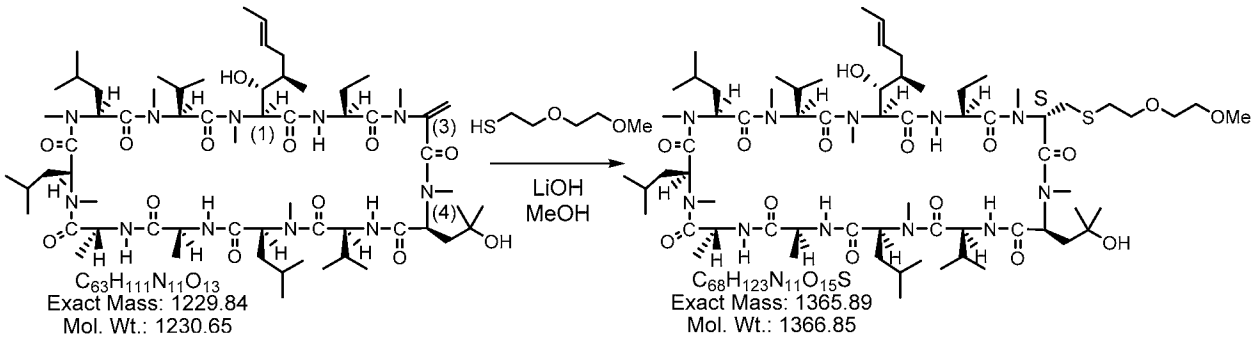
[(S)-(2-(2-Hydroxyethoxy)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



To a suspension of [(S)-((ethoxycarbonylmethoxy)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (100 mg, 0.07 mmol) and lithium chloride (15 mg, 0.35 mmol) in methanol (10 ml) was added sodium borohydride (125 mg, 3.29 mmol) in portions. The mixture was stirred overnight at room temperature for 6 hours. Most of solvent was evaporated under reduced pressure. Dichloromethane (50 ml) and water (200 ml) were added and separated. The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give the product [Molecular formula: $C_{67}H_{121}N_{11}O_{15}S$; Exact Mass: 1351.88; MS (m/z): 1352.46 $(M+1)^+$; TLC R_f: 0.32 (dichloromethane/methanol = 95/5); HPLC RT: 12.87 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 54

[(S)-(2-(2-Methoxyethoxy)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

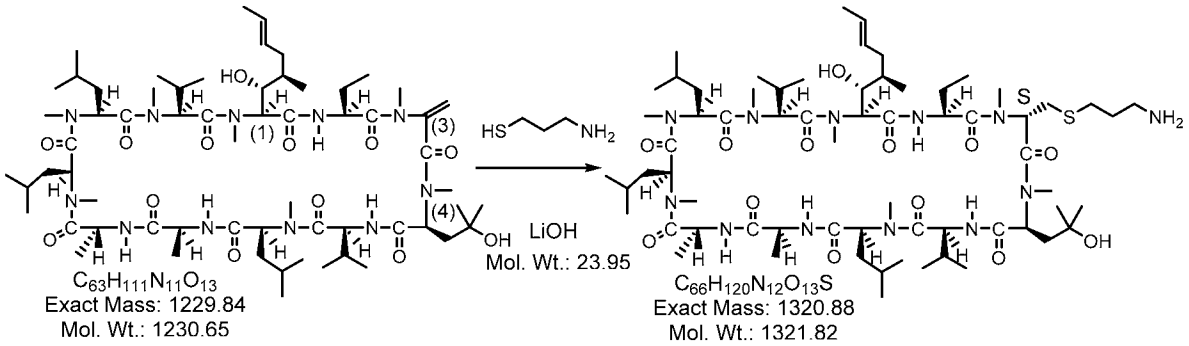


To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (300 mg, 0.24 mmol) and 2-(2-methoxyethoxy)ethanethiol (330 mg, 2.42 mmol) in methanol (20 ml) was added lithium hydroxide (60 mg, 2.50 mmol). The reaction mixture was stirred at

room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate/methanol = 97/3) to give a pure product [Molecular formula: $C_{68}H_{123}N_{11}O_{15}S$; Exact Mass: 1365.89; MS (m/z): 1366.49 $(M+1)^+$; TLC Rf: 0.37 (dichloromethane/methanol = 97/3); HPLC RT: 14.72 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 55

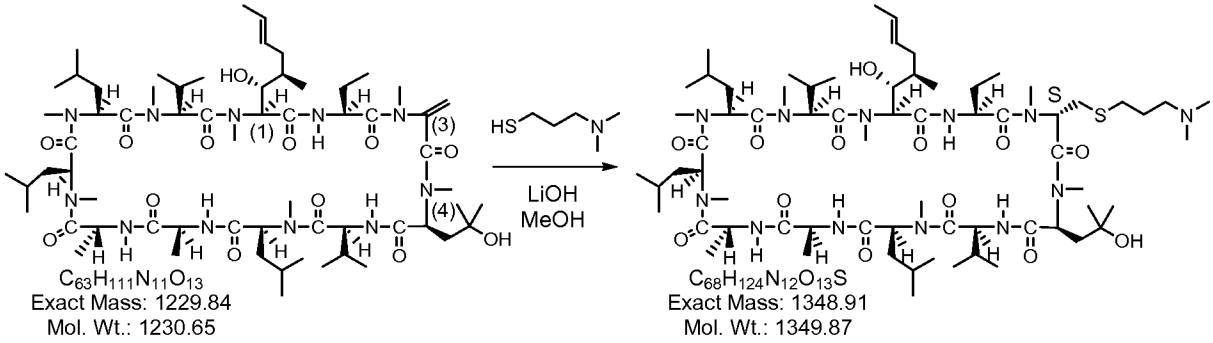
[(S)-(3-Aminopropylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0222] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (3.00 g, 2.44 mmol) and 3-aminopropanethiol (1.33 g, 14.59 mmol) were dissolved in methanol (80 ml), followed by adding lithium hydroxide (0.35 g, 14.65 mmol). The mixture was stirred at room temperature for a weekend. After removal of solvent, the residue was purified by chromatography using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{66}H_{120}N_{12}O_{13}S$; Exact Mass: 1320.88; MS (m/z): 1321.52 $(M+1)^+$, 1343.67 $(M+Na)^+$, TLC R_f: 0.028 (dichloromethane/methanol = 5/1); HPLC RT: 10.24 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 56

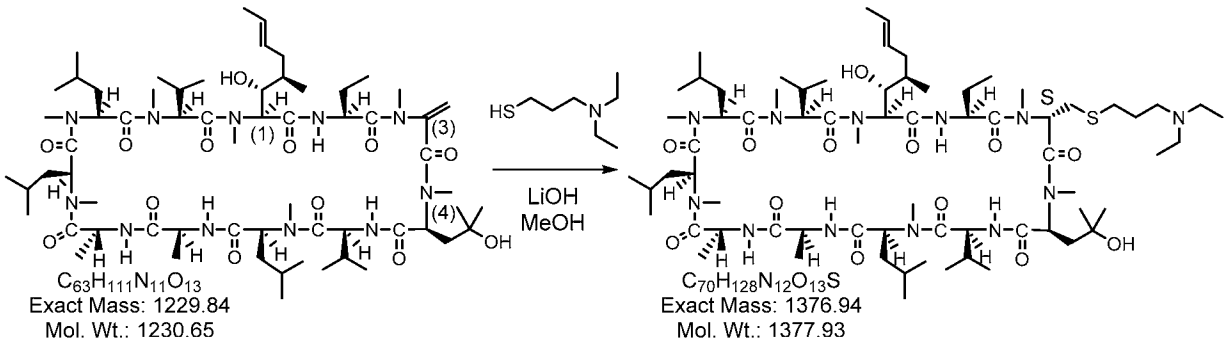
[(S)-(3-(N,N-Dimethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0223] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.30 g, 0.24 mmol) and 3-(N,N-dimethyl)propylthiol (0.36 g, 2.40 mmol) were dissolved in methanol (25 ml), followed by adding lithium hydroxide (59 mg, 2.44 mmol). The mixture was stirred at room temperature overnight. After removal of solvent, the residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.18 g of pure product [Molecular Formula: $C_{68}H_{124}N_{12}O_{13}S$; Exact Mass: 1348.91; MS (m/z): 1349.70 $(M+1)^+$, 1371.83 (M+Na); TLC R_f: 0.15 (ethyl acetate/methanol = 5/1); HPLC RT: 11.53 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 57

[(S)-(3-(N,N-Diethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

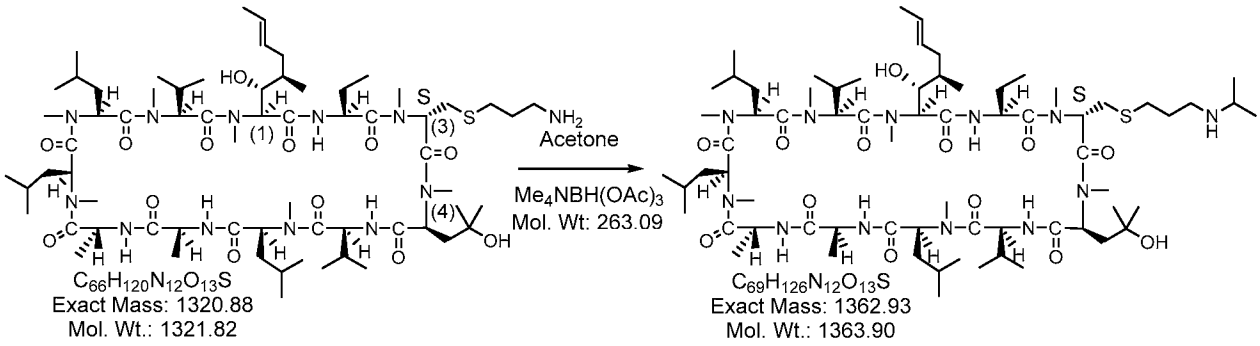


[0224] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.30 g, 0.24 mmol) and 3-(N,N-dimethyl)propylthiol (0.36 g, 2.44 mmol) were dissolved in methanol (25 ml), followed by adding lithium chloride (59 mg, 2.4 mmol). The mixture was stirred at room temperature overnight. After removal of solvent, the residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.30 g of product

[Molecular Formula: $C_{70}H_{128}N_{12}O_{13}S$; Exact Mass: 1376.94; MS (m/z): 1377.90 $(M+1)^+$, 1399.76 $(M+Na)^+$; TLC R_f: 0.17 (ethyl acetate/methanol = 5/1); HPLC RT: 12.06 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 58

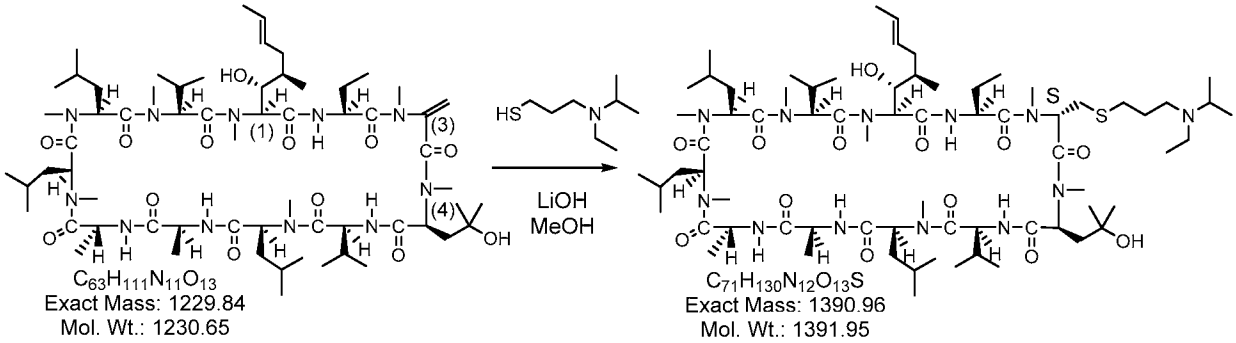
[(S)-(3-(N-Isopropylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0225] [(S)-(3-Aminopropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.11 mmol) and acetone (MW 58.08, d 0.791, 42 μl, 0.57 mmol) were dissolved in 10 ml of dichloromethane, followed by adding tetramethylammonium triacetoxyborohydride (74.7 mg, 0.28 mmol) in portions and a few drops of acetic acid. The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{69}H_{126}N_{12}O_{13}S$; Exact Mass: 1362.93; MS (m/z): 1363.60 $(M+1)^+$; TLC R_f: 0.38 (dichloromethane/methanol = 9/1); HPLC RT: 10.89 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 59

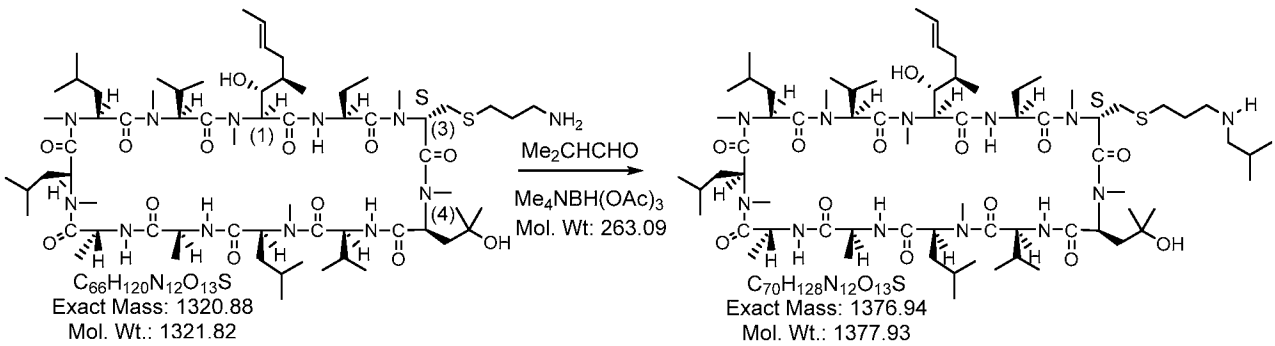
[(S)-(3-(N-Ethyl-N-isopropylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0226] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (200 mg, 0.16 mmol) and 3-(N-ethyl-N-isopropylamino)propylthiol (200 mg, 1.25 mmol) in methanol (25 ml) was added lithium hydroxide (89 mg, 3.71 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give 88 mg of product [Molecular Formula: $C_{71}H_{130}N_{12}O_{13}S$; Exact Mass: 1390.96; MS (m/z): 1413.81 $(M+Na)^+$; TLC Rf: 0.40 (dichloromethane/methanol = 9/1); HPLC RT: 12.49 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 60

[(S)-(3-(N-Isobutylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

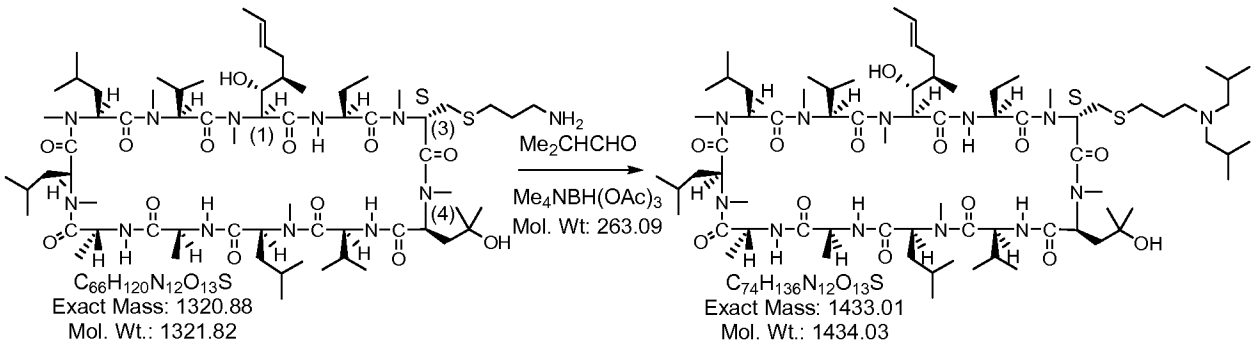


[0227] [(S)-(3-Aminopropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.11 mmol) and isobutyraldehyde (MW 72.11, d 0.794, 15 μl, 0.17 mmol) were

dissolved in dichloromethane (25 ml), followed by adding a few drops of acetic acid and tetramethylammonium triacetoxyborohydride (30 mg, 0.11 mmol) in portions. The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with saturated sodium bicarbonate solution (25 ml) and brine (25 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{70}H_{128}N_{12}O_{13}S$; Exact Mass: 1376.94; MS (m/z): 1477.56 $(M+1)^+$, 1399.71 $(M+Na)^+$; TLC R_f: 0.18 (dichloromethane/methanol = 9:1); HPLC RT: 11.70 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 61

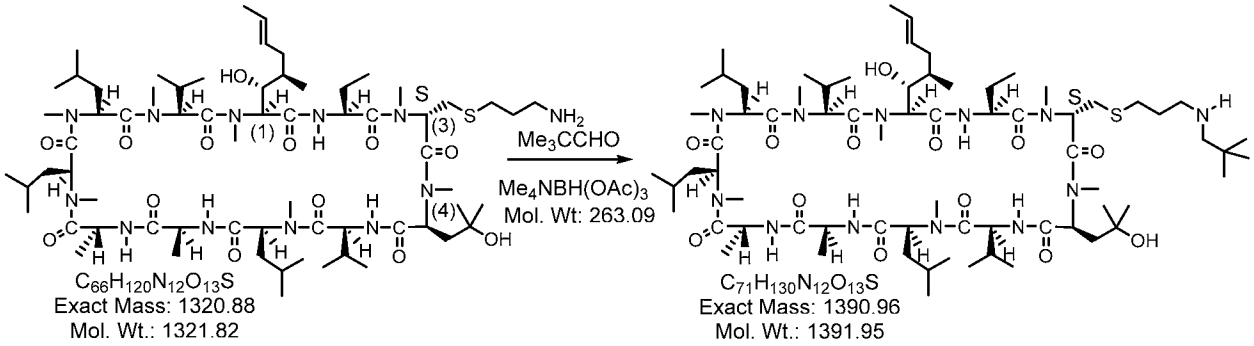
[(S)-(3-(N,N-Diisobutylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0228] [(S)-(3-Aminopropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.11 mmol) and isobutyraldehyde (MW 72.11, d 0.794, 15 μl, 0.17 mmol) were dissolved in dichloromethane (25 ml), followed by adding a few drops of acetic acid and tetramethylammonium triacetoxyborohydride (30 mg, 0.11 mmol in portions. The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with saturated sodium bicarbonate solution (25 ml) and brine (25 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{73}H_{134}N_{12}O_{13}S$; Exact Mass: 1433.01; MS (m/z): 1433.64 $(M+1)^+$, 1455.78 $(M+Na)^+$; TLC R_f: 0.24 (dichloromethane/methanol = 95:5); HPLC RT: 14.45 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 62

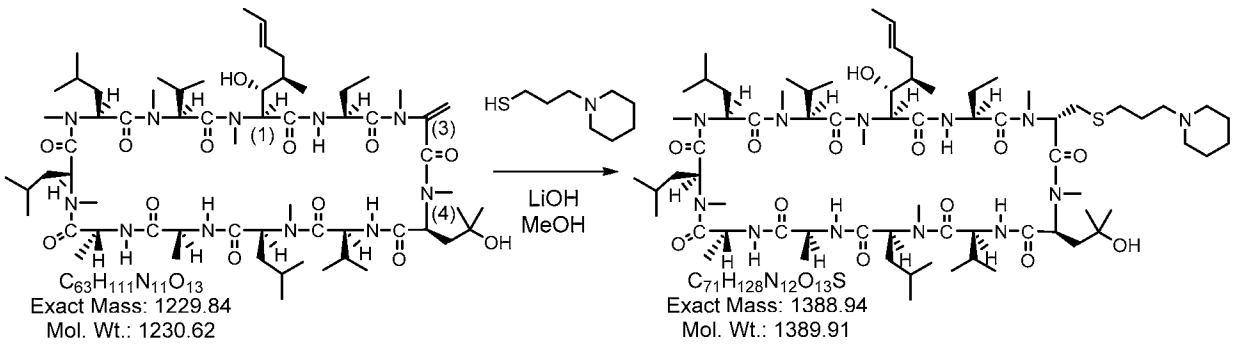
[(S)-(3-(N-Neopentylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0229] [(S)-(3-Aminopropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (50 mg, 0.04 mmol) and pivalaldehyde (MW 86.13, d 0.793, 21 μl, 0.19 mmol) were mixed with 20 ml of dichloromethane, followed by adding tetramethylammonium triacetoxyborohydride (24.9 mg, 0.10 mmol) and a few drops of acetic acid. The mixture was stirred at room temperature for 6 hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution (30 ml) and brine (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{71}H_{130}N_{12}O_{13}S$; Exact Mass: 1390.96; MS (m/z): 1391.54 $(M+1)^+$, 1413.69 $(M+Na)^+$; TLC R_f: 0.24 (dichloromethane/methanol = 5/1); HPLC RT: 13.21 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 63

[(S)-(3-(N-Piperidinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

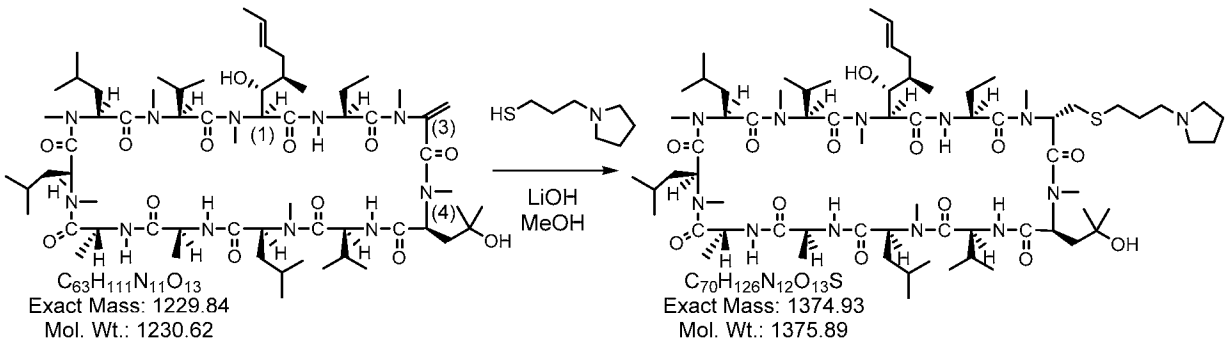


[0230] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.20 mmol) and 3-(N-piperidinyl)propanethiol (318 mg, 2.00 mmol) in methanol (30 ml) was added lithium hydroxide (96 mg, 4.00 mmol). The reaction mixture was stirred

at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 135 mg of product [Molecular Formula: $C_{71}H_{128}N_{12}O_{13}S$; Exact Mass: 1388.94; MS (m/z): 1389.84 $(M+1)^+$; TLC Rf: 0.30 (dichloromethane/methanol = 95/5); HPLC RT: 12.19 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm); ^1H NMR spectrum (600 MHz, $CDCl_3$, δ in ppm): 0.68 (d, J=6.0Hz, 3H), 0.79 (d, J=6.0Hz, 3H), 0.82-0.86 (m, 9H), 0.88 (d, J=6.6Hz, 3H), 0.91 (d, J=6.6Hz, 3H), 0.93 (d, J=6.6Hz, 3H), 0.97-1.00 (m, 9H), 1.09 (d, J=6.6Hz, 3H), 1.21-1.24 (m, 11H), 1.31-1.46 (m, 8H), 1.53 (m, 5H), 1.61 (m, 11H), 1.67-1.70 (m, 2H), 1.74-1.76 (m, 2H), 1.99-2.11 (m, 4H), 2.31-2.35 (m, 4H), 2.37-2.41 (m, 2H), 2.53-2.60 (m, 2H), 2.67 (s, 6H), 2.91-2.98 (m. 2H), 3.09 (s, 3H), 3.24 (s, 6H), 3.26 (s, 3H), 3.48 (s, 3H), 3.56 (m, 1H), 3.65 (m, 1H), 4.51 (m, 1H), 4.58 (t, J=8.4Hz, 1H), 4.81 (m, 1H), 4.94-5.02 (m, 2H), 5.04 (t, J=6.6Hz, 1H), 5.08 (d, J=10.8Hz, 1H), 5.28-5.32 (m, 1H), 5.33-5.37 (m, 1H), 5.49 (m, 2H), 5.67 (dd, J=10.8Hz and 3.6Hz, 1H), 7.14 (d, J=8.4Hz, 1H), 7.49 (d, J=8.4Hz, 1H), 7.64 (d, J=8.4Hz, 1H), 8.09 (d, J=10.2Hz, 1H)].

Example 64

[(S)-(3-(N-Pyrrolidinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

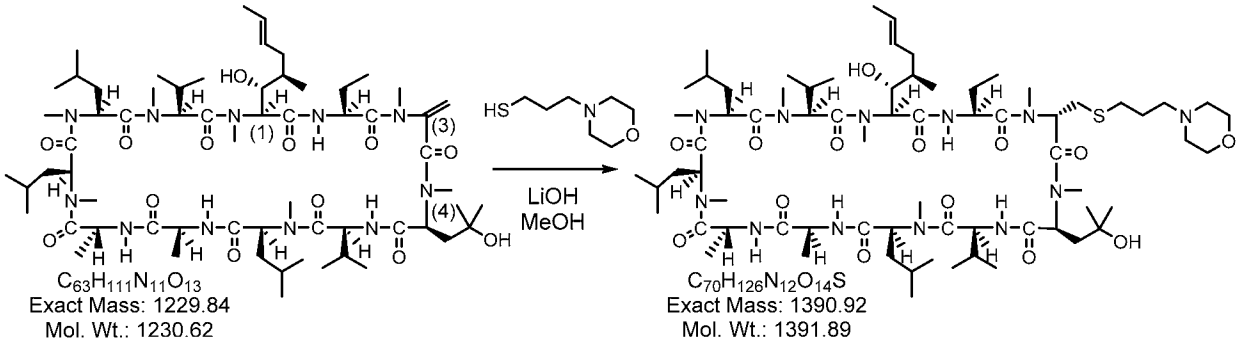


[0231] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (213 mg, 0.17 mmol) and 3-(N-pyrrolidinyl)propanethiol (280 mg, 1.93 mmol) in methanol (25 ml) was added lithium hydroxide (94mg, 3.92 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium

sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 95/5) to give 57 mg of product [Molecular Formula: $C_{70}H_{126}N_{12}O_{13}S$; Exact Mass: 1374.93; MS (m/z): 1375.75 $(M+1)^+$; TLC Rf: 0.23 (dichloromethane/methanol = 95/5); HPLC RT: 11.83 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 65

[(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

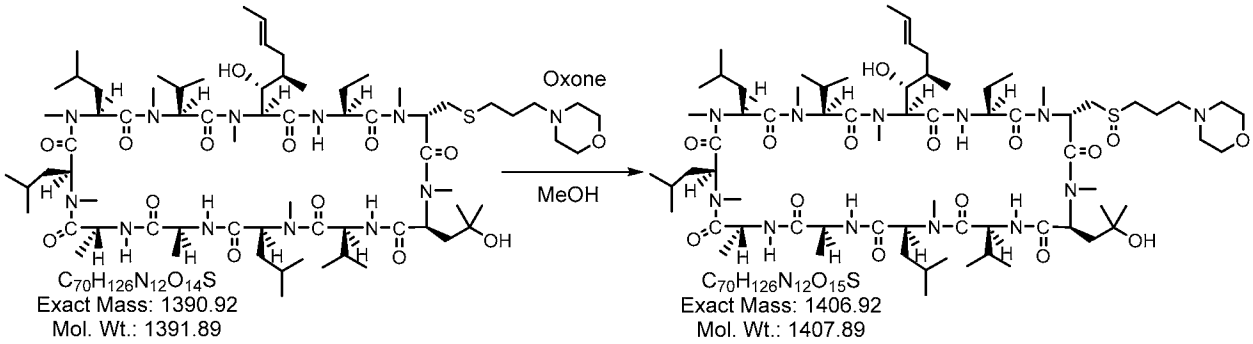


[0232] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (210 mg, 0.17 mmol) and 3-morpholinopropanethiol (300 mg, 1.86 mmol) in methanol (25 ml) was added lithium hydroxide (140 mg, 5.83 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give 78 mg of product [Molecular Formula: $C_{70}H_{126}N_{12}O_{14}S$; Exact Mass: 1390.92; MS (m/z): 1413.77 $(M+Na)^+$; TLC Rf: 0.33 (dichloromethane/methanol = 9/1); HPLC RT: 11.35 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm); ^1H NMR spectrum (600 MHz, $CDCl_3$, δ in ppm): 0.68 (d, J=6.0Hz, 3H), 0.79 (d, J=5.4Hz, 3H), 0.82-0.86 (m, 9H), 0.88 (d, J=6.6Hz, 3H), 0.91 (d, J=6.6Hz, 3H), 0.93 (d, J=6.6Hz, 3H), 0.97-1.00 (m, 9H), 1.09 (d, J=6.6Hz, 3H), 1.21-1.24 (m, 11H), 1.31 (d, J=7.2Hz, 3H), 1.38-1.46 (m, 2H), 1.61 (m, 11H), 1.67-1.70 (m, 2H), 1.74-1.76 (m, 2H), 2.03-2.11 (m, 4H), 2.35-2.43 (m, 8H), 2.55-2.63 (m, 2H), 2.67 (s, 6H), 2.91-2.98 (m. 2H), 3.10 (s, 3H), 3.24 (3, 6H), 3.26 (s, 3H), 3.49 (s, 3H), 3.52 (m, 1H), 3.65-3.67 (m, 5H), 4.51 (m, 1H), 4.59 (t, J=8.4Hz, 1H), 4.81 (m, 1H), 4.94-5.01 (m, 2H), 5.04 (t, J=6.6Hz, 1H),

5.08 (d, J=12Hz, 1H), 5.28-5.30 (m, 1H), 5.33-5.37 (m, 1H), 5.49 (m, 2H), 5.67 (m, 1H), 7.14 (d, J=7.8Hz, 1H), 7.49 (d, J=8.4Hz, 1H), 7.65 (d, J=7.2Hz, 1H), 8.12 (d, J=9.6Hz, 1H)].

Example 66

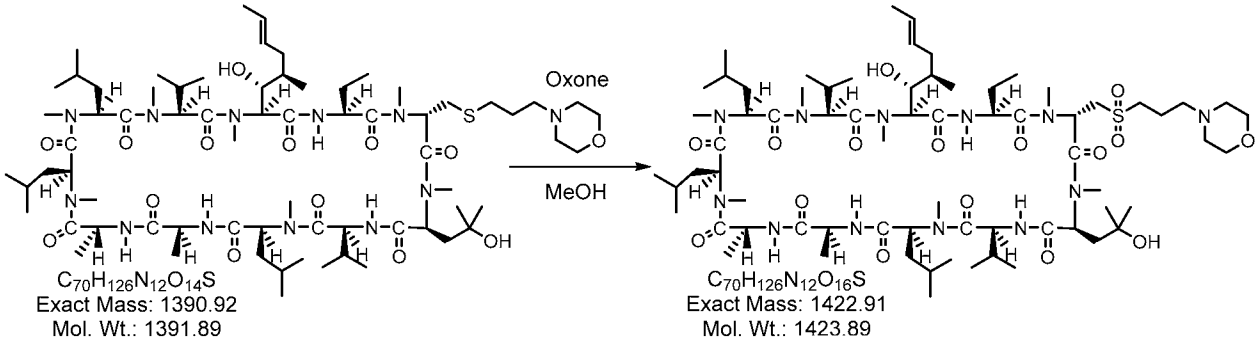
[(S)-(3-(N-Morpholino)propylsulfinyl)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0233] To a solution of [(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-hydroxyl)-N-MeLeu]-4-cyclosporin (27 mg, 0.02 mmol) in methanol (5 ml) was added oxone (25 mg, 0.04 mmol). The reaction mixture was stirred at room temperature for one hour. Then most of the solvent was evaporated under reduced pressure. Dichloromethane (20 ml) and saturated sodium bicarbonate solution (5 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give product [Molecular formula: $C_{70}H_{126}N_{12}O_{15}S$; Exact Mass: 1406.92; MS (m/z): 1407.47 $(M+1)^+$; TLC Rf: 0.23 (dichloromethane/methanol = 9/1); HPLC RT: 9.35 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 67

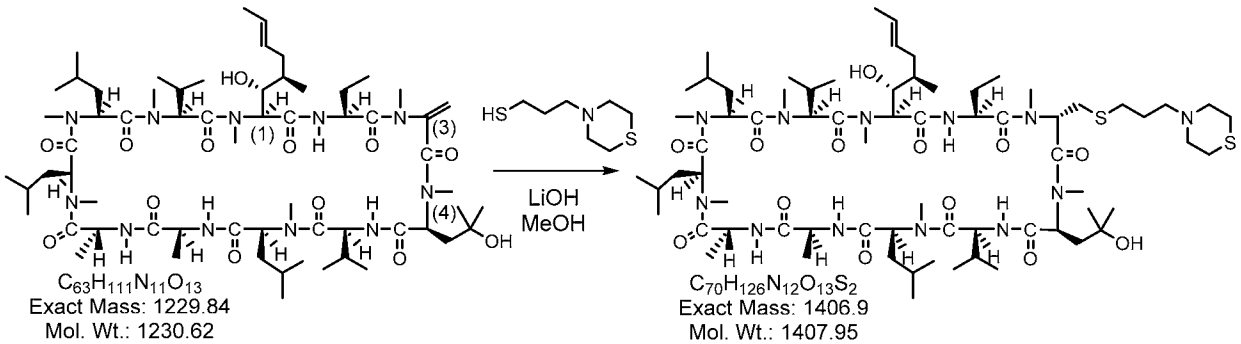
[(S)-(3-(N-Morpholino)propylsulfonyl)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0234] To a solution of [(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-hydroxyl)-N-MeLeu]-4-cyclosporin (30 mg, 0.02 mmol) in methanol (5 ml) were added oxone (40 mg, 0.07 mmol) and water (0.3 ml) at 0 °C. The reaction mixture was stirred at room temperature 1 hour. Dichloromethane (30 ml) and cold saturated sodium bicarbonate solution (5 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give product [Molecular formula: $C_{70}H_{126}N_{12}O_{16}S$; Exact Mass: 1422.91; MS (m/z): 1423.54 $(M+1)^+$; TLC Rf: 0.28 (dichloromethane/methanol = 9/1); HPLC RT: 9.38 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 68

[(S)-(3-(N-Thiomorpholino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

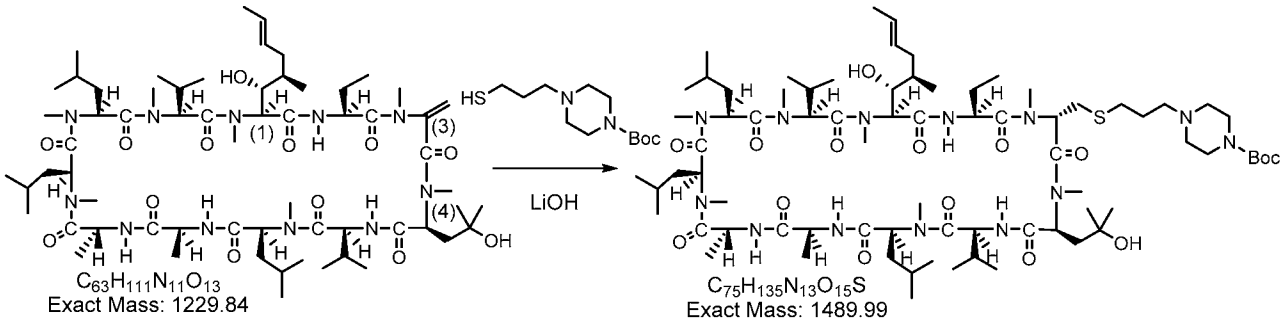


[0235] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (280 mg, 0.23 mmol) and 4-(3-thiopropyl)thiomorpholine (280 mg, 1.58 mmol) in methanol (15 ml) was added lithium hydroxide (80 mg, 3.33 mmol). The reaction mixture

was stirred at room temperature overnight. Then most of the solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give product [Molecular formula: $C_{70}H_{126}N_{12}O_{13}S_2$; Exact Mass: 1406.90; MS (m/z): 1407.51 $(M+1)^+$; TLC Rf: 0.35 (dichloromethane/methanol = 9/1); HPLC RT: 11.18 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 69

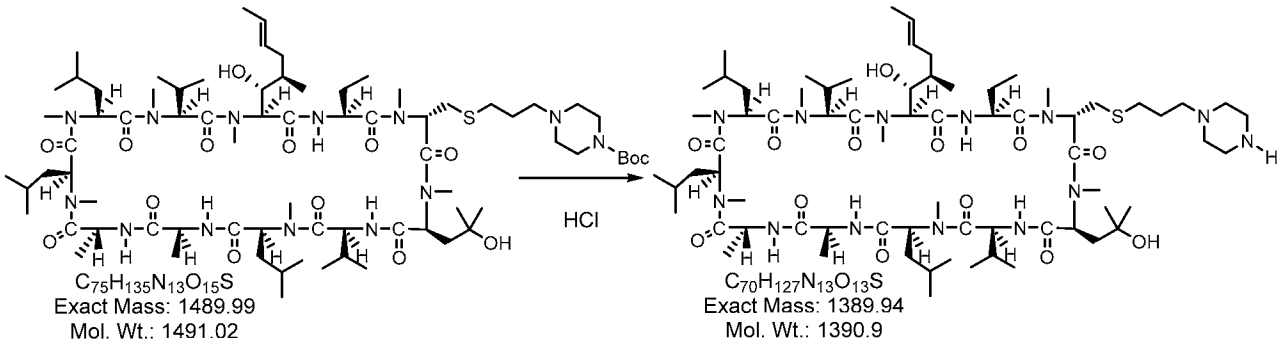
[(S)-(3-(4-N-Boc-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0236] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (2.95 g, 2.40 mmol) and 1-Boc-4-(3-mercaptopropanyl)piperazine (MW: 260.4, 3.18 g, 5.10 mmol) were dissolved in methanol (75 ml), followed by adding lithium hydroxide (MW: 23.95, 0.35 g, 14.4 mmol). The mixture was stirred at room temperature overnight. After removal of solvent, the residue was purified by chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{75}H_{135}N_{13}O_{15}S$; Exact Mass: 1489.99; MS (m/z): 1490.54 $(M+1)^+$, 1512.63 $(M+Na)^+$; HPLC RT: 12.51 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 70

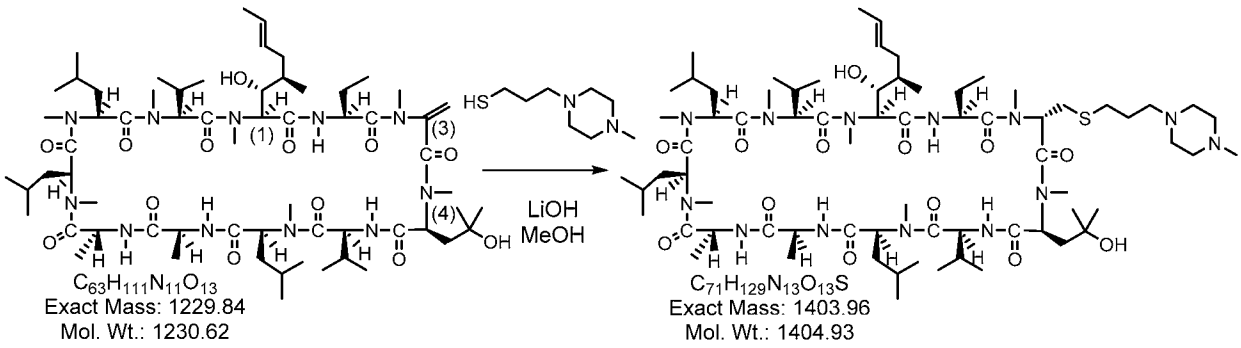
[(S)-(3-(N-Piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0237] [(R)-(3-(4-N-Boc-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (1.59 g, 1.07 mmol) was dissolved in methanol (20 ml). Then 4 M hydrochloric acid in dioxane (4 ml) was added. The mixture was stirred at room temperature for one hour. Most of solvent was evaporated under reduced pressure. The residue was mixed ethyl acetate (60 ml) and saturated sodium bicarbonate solution (60 ml) and separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular Formula: $C_{70}H_{127}N_{13}O_{13}S$; Exact Mass: 1389.94; MS (m/z): 1390.56 $(M+1)^+$, 1412.70 $(M+Na)^+$; TLC R_f: 0.37 (dichloromethane/methanol = 5:1); HPLC RT: 8.20 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 71

[(S)-(3-(4-Methyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

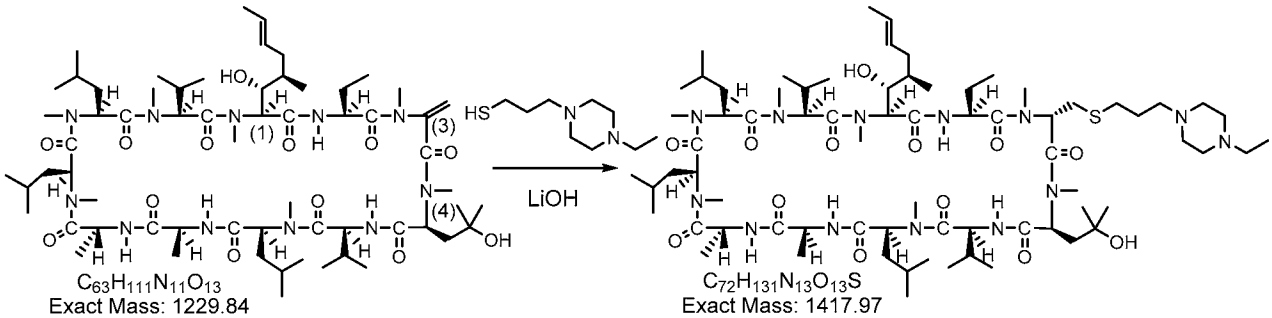


[0238] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.30 g, 0.24 mmol) and 3-(4-methylpiperazino)propylthiol (MW: 174.31, 0.42 g, 2.44 mmol) were dissolved in methanol (25 ml), followed by adding 10 equivalents of lithium hydroxide (58 mg, 2.40 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by flash chromatography using dichloromethane/methanol

as eluent to give 0.20 g of product [Molecular Formula: $C_{71}H_{129}N_{13}O_{13}S$; Exact Mass: 1403.96; MS (m/z): 1404.9 $(M+1)^+$, 1426.9 $(M+Na)^+$; TLC R_f: 0.10 (ethyl acetate/methanol = 5/1); HPLC RT: 10.07 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 72

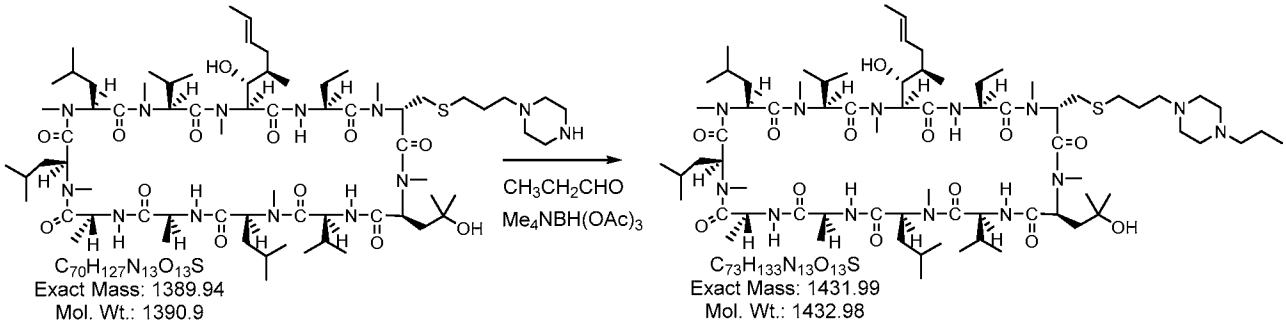
[(S)-(3-(4-Ethyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0239] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) and 3-(1-ethyl-4-piperazino)propylthiol (MW: 188.33, 0.20 g, 1.06 mmol) were dissolved in methanol (15 ml), followed by adding lithium hydroxide (MW: 23.95, 48 mg, 20 mmol). The mixture was stirred overnight at room temperature. After removal of solvents, the residue was subject to chromatography using dichloromethane/methanol as eluent to give product [Molecular formula: $C_{72}H_{131}N_{13}O_{13}S$; Exact Mass: 1417.97; MS (m/z): 1418.58$(M+1)^+$; TLC R_f: 0.13 (ethyl acetate/methanol = 5/1)]. HPLC RT: 8.70 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 73

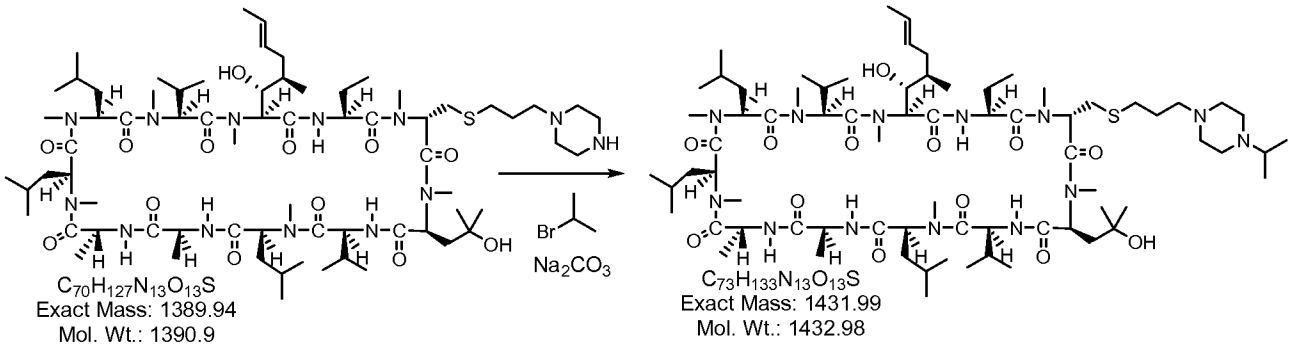
[(S)-(3-(4-N-n-Propyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0240] [(S)-(3-(N-Piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.11 mmol) and propionaldehyde (MW 58.08, d 0.81, 80 µl, 1.11 mmol) were dissolved in dichloromethane (20 ml), followed by adding acetic acid (5 drops) and tetramethylammonium triacetoxyborohydride (MW: 263.09, 72 mg, 0.28 mmol) in portions. The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and methanol as eluent to give product [Molecular Formula: $C_{73}H_{133}N_{13}O_{13}S$; Exact Mass: 1431.99; MS (m/z): 1432.61 $(M+1)^+$, 1454.69 $(M+Na)^+$; TLC R_f: 0.24 (dichloromethane/methanol = 9:1); HPLC RT: 9.07 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 74

[(S)-(3-(4-N-Isopropyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

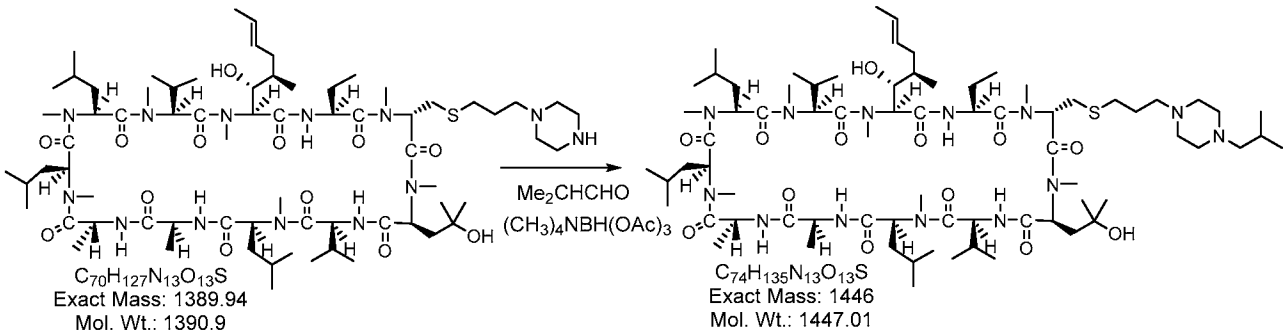


[0241] [(S)-3-(N-Piperazinylpropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin(150 mg, 0.11 mmol) and 2-bromopropane (MW 123.00, d 1.310, 102 µl, 1.08

mmol) were dissolved in dichloromethane (15 ml), followed by adding sodium carbonate (MW: 105.99, 28.6 mg, 0.27 mmol). The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and methanol as eluent to give product [Molecular Formula: $C_{73}H_{135}N_{13}O_{13}S$; Exact Mass: 1431.99; MS (m/z): 1432.58 $(M+1)^+$, 1454.72 $(M+Na)^+$; TLC R_f: 0.14 (dichloromethane/methanol = 9:1); HPLC RT: 8.74 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 75

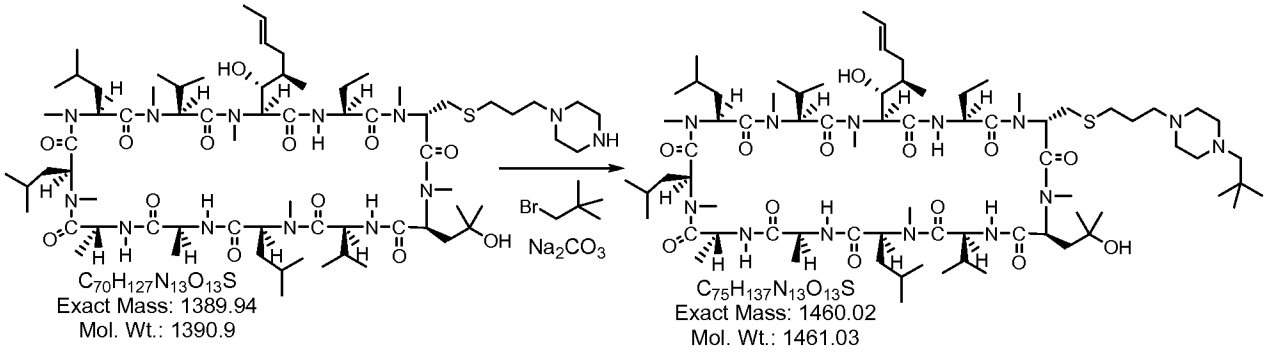
[(S)-(3-(4-N-Isobutyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0242] [(S)-3-(N-Piperazinylpropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (168 mg, 0.12 mmol) and isobutyraldehyde (MW 72.11, d 0.794, 110 μl, 1.21 mmol) were dissolved in dichloromethane (25 ml), followed by adding acetic acid (5 drops) and tetramethylammonium triacetoxyborohydride (79.5 mg, 0.30 mmol) in portions. The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and methanol as eluent to give product [Molecular Formula: $C_{74}H_{135}N_{13}O_{13}S$; Exact Mass: 1446.00; MS (m/z): 1446.58 $(M+1)^+$, 1468.69 $(M+Na)^+$; TLC R_f: 0.43 (dichloromethane/methanol = 9:1); HPLC RT: 9.59 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 76

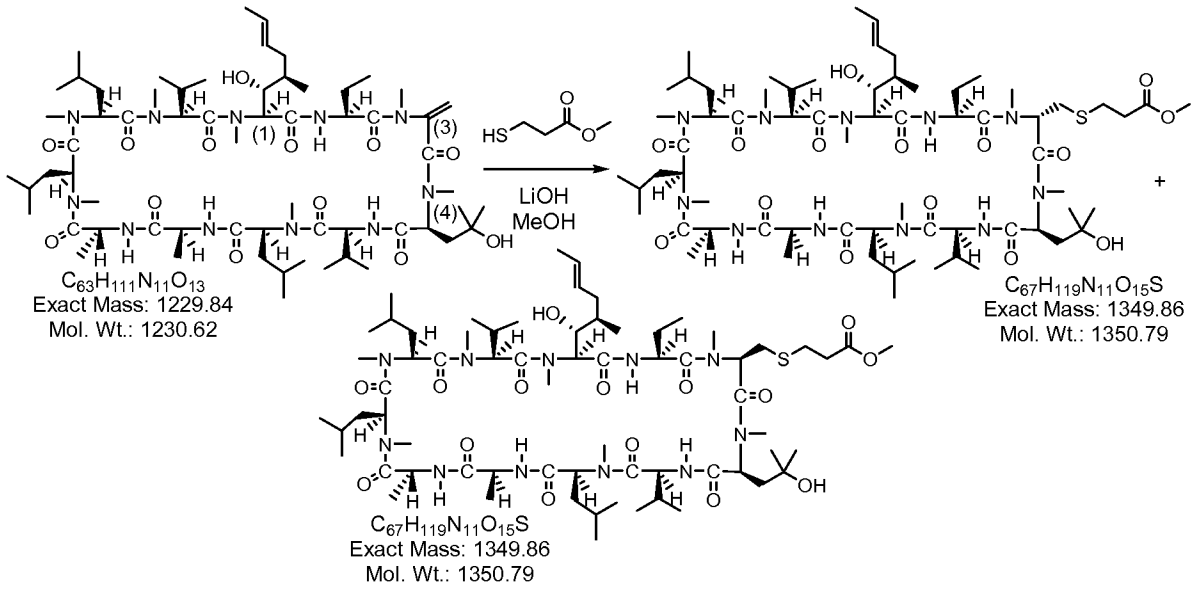
[(S)-(3-(4-N-Neopentyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0243] [(S)-3-(N-Piperazinylpropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.11 mmol) and neopentyl bromide (MW 151.05, d 1.195, 136 μl, 1.08 mmol) were dissolved in dichloromethane (20 ml), followed by adding sodium carbonate (MW: 105.99, 28.6 mg, 0.27 mmol). The mixture was stirred at room temperature overnight. Then the reaction mixture was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using dichloromethane and methanol as eluent to give product [Molecular Formula: $C_{75}H_{137}N_{13}O_{13}S$; Exact Mass: 1460.02; MS (m/z): 1460.64 $(M+1)^+$, 1482.72 $(M+Na)^+$; TLC R_f: 0.43 (dichloromethane/methanol = 9:1); HPLC RT: 11.25 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 77

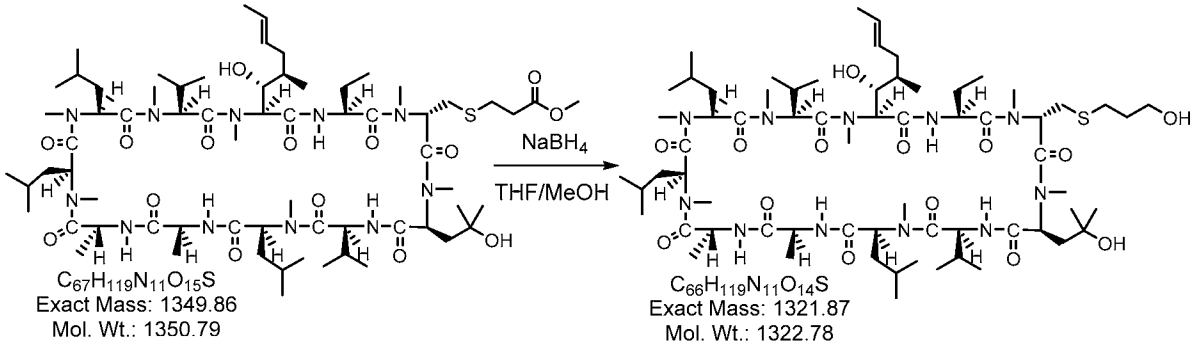
[(S)-(2-(Methoxycarbonyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin and [(R)-(2-(Methoxycarbonyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



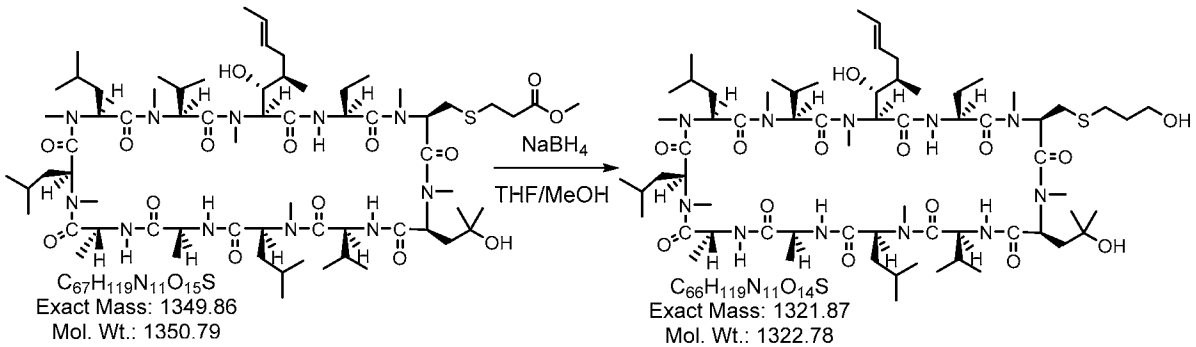
[0244] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (600 mg, 0.49 mmol) and methyl 3-mercaptopropionate (0.54 ml, d 1.085, 4.88 mmol) in methanol (15 ml) was added lithium hydroxide (94 mg, 3.90 mmol). The reaction mixture was stirred at room temperature for 4 hours. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and brine (30 ml) were added and the mixture was separated. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone) to give 270 mg of [(S)-(2-(methoxycarbonyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{67}H_{119}N_{11}O_{15}S$; Exact Mass: 1349.86. MS (m/z): 1350.43$(M+1)^+$, 1372.62 $(M+Na)^+$] and 260 mg of [(R)-(2-(methoxycarbonyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{67}H_{119}N_{11}O_{15}S$; Exact Mass: 1349.86. MS (m/z): 1350.42$(M+1)^+$, 1372.63 $(M+Na)^+$].

Example 78

[(S)-(3-Hydroxylpropylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin and [(R)-(3-Hydroxylpropylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0245] [(S)-(2-(Methoxycarbonyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (170 mg, 0.13 mmol) was dissolved in tetrahydrofuran (30 ml), followed by adding cesium chloride (1.00 g, 5.94 mmol) and sodium borohydride (1.00 g, 26.43 mmol). Then 30 ml of methanol was added dropwise to the mixture over 30 minutes. After addition, the mixture was stirred at room temperature one hour. Most solvent was then evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography with dichloromethane/methanol (from 100:0 to 96:4) as eluent to give the 55 mg of pure product [Molecular Formula: $C_{66}H_{119}N_{11}O_{14}S$; Exact Mass: 1321.87; MS (m/z): 1322.45 $(M+1)^+$, 1344.67 $(M+Na)^+$; TLC R_f: 0.54 (dichloromethane/methanol = 9:1); HPLC RT: 13.06 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

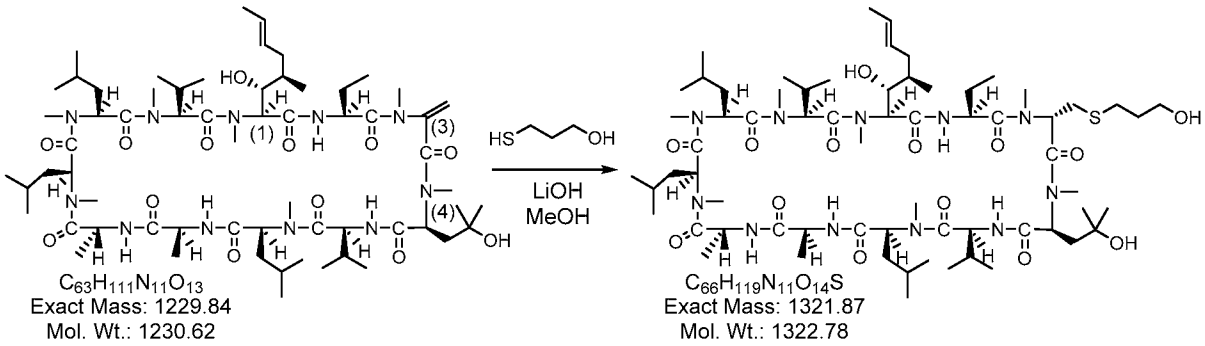


[0246] According this method, 28 mg of pure [(R)-(3-Hydroxypropylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{66}H_{119}N_{11}O_{14}S$; Exact Mass: 1321.87; MS (m/z): 1322.44 $(M+1)^+$, 1344.69 $(M+Na)^+$; TLC R_f: 0.54 (dichloromethane/methanol = 9:1); HPLC RT: 13.02 min (C8 reverse phase column: 250

mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)]was obtained.

Example 79

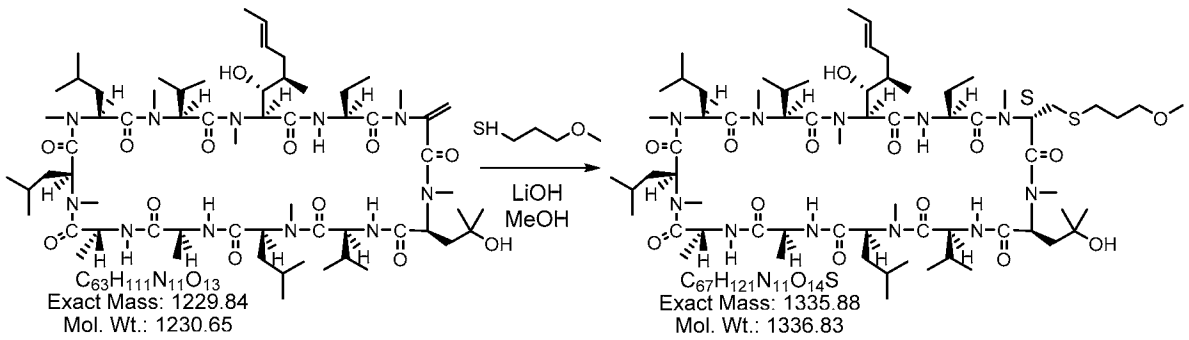
[(S)-(3-Hydroxylpropylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0247] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (200 mg, 0.16 mmol) and 3-mercapto-1-propanol (125 mg, 1.36 mmol) in methanol (15 ml) was added lithium hydroxide (80 mg, 3.33 mmol). The reaction mixture was stirred at room temperature overnight. Then most of the solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give product of [(R)-(3-Hydroxypropylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular formula: $C_{66}H_{119}N_{11}O_{14}S$; Exact Mass: 1321.87; MS (m/z): 1322.53 $(M+1)^+$; TLC Rf: 0.54 (dichloromethane/methanol = 9/1); HPLC RT: 13.02 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 80

[(S)-(3-Methoxypropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

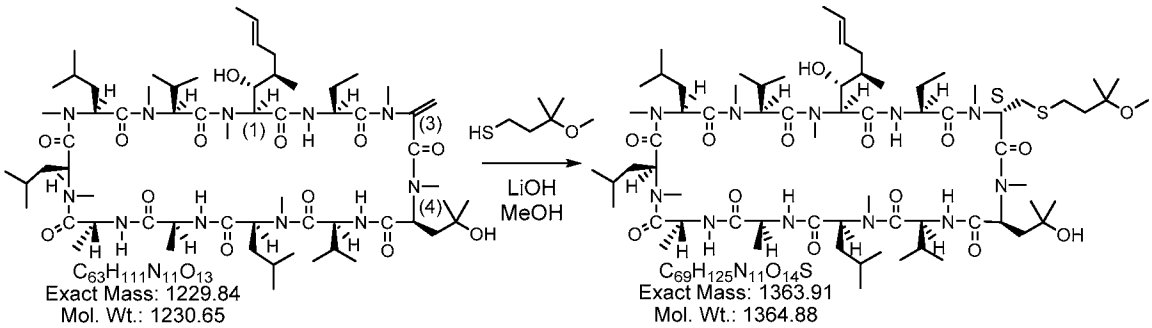


[0248] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.31 g, 0.25 mmol) and 1-mercapto-3-methoxypropane (265 mg, 10 mmol) were dissolved in methanol

(10 ml), followed by adding 10 equivalents of lithium hydroxide (60 mg). The mixture was stirred overnight at room temperature. After removal of solvents, the residue was dissolved in ethyl acetate (15 ml). The ethyl acetate solution was washed with brine, dried over magnesium sulfite and evaporated under reduced pressure. The residue was subject to a flash chromatography using ethyl acetate/methanol as eluent to give 35 mg of pure product [Molecular formula: $C_{67}H_{121}N_{11}O_{14}S$; Exact Mass: 1335.88; MS (m/z): 1336.43 $(M+1)^+$, 1358.74 $(M+Na)^+$; TLC R_f: 0.31 (ethyl acetate/methanol = 20/1); HPLC RT: 15.21 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 81

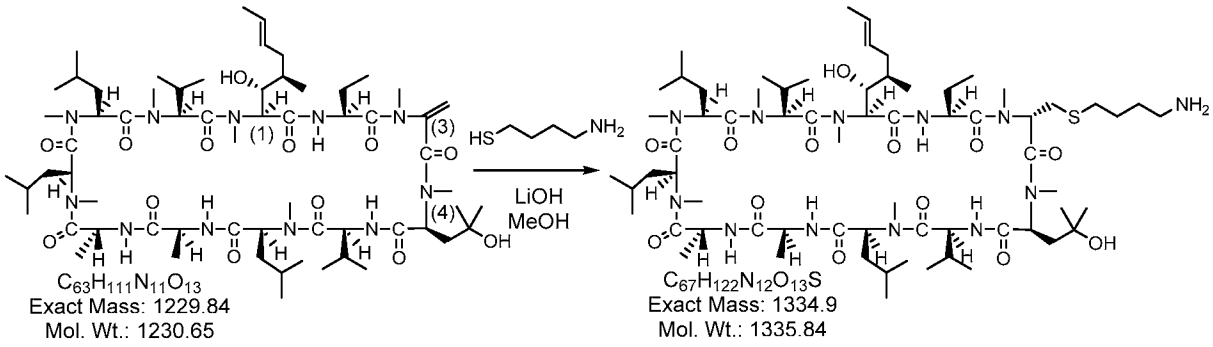
[(S)-(3-Methoxy-3-methyl)butylthiomethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[0249] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.12 mmol) and 3-methyl-3-methoxybutanethiol (165 mg, 1.23 mmol) in methanol (10 ml) was added lithium hydroxide (50 mg, 2.08 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate/methanol = 98/2) to give a pure product [Molecular formula: $C_{69}H_{125}N_{11}O_{14}S$; Exact Mass: 1363.91; MS (m/z): 1364.53 $(M+1)^+$; TLC Rf: 0.33 (ethyl acetate/methanol = 98/2); HPLC RT: 16.10 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 82

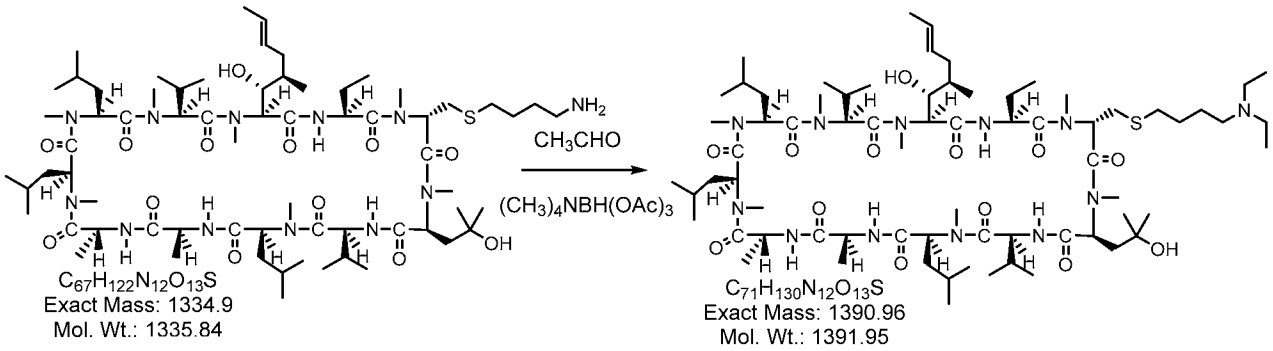
[(S)-(4-Aminobutylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0250] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (1.23 g, 1.0 mmol) and 4-aminobutylthiol (1.06 g, 10.00 mmol) were dissolved in methanol (80 ml), followed by adding 10 equivalents of lithium hydroxide (0.24 g, 10.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvents, the residue was subjected to the flash chromatography using dichloromethane/methanol as eluents to give 0.40 g of product [Molecular formula: $C_{67}H_{122}N_{12}O_{13}S$; Exact Mass: 1334.89; MS (m/z): 1335.55 $(M+1)^+$, 1357.64 $(M+Na)^+$, TLC R_f: 0.05 (dichloromethane/methanol = 5/1); HPLC RT: 10.53 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 83

[(S)-(4-(N,N-Diethylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

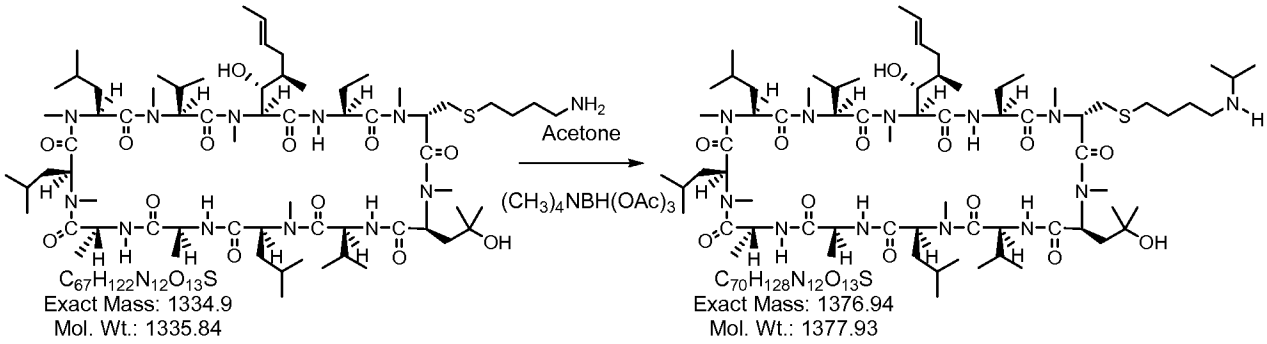


[0251] [(S)-(4-Aminobuylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (70 mg, 0.05 mmol) and acetaldehyde (MW 44.05, d 0.78, 100 μl, 0.18 mmol)) were dissolved in chloroform (5 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (32.87 mg, 0.125 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with

saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular formula: $C_{71}H_{130}N_{12}O_{13}S$; Exact Mass: 1390.96; MS (m/z): 1391.63$(M+1)^+$, 1413.79 $(M+Na)^+$; TLC R_f: 0.17 (ethyl acetate/methanol = 5/1); HPLC RT: 12.55 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 84

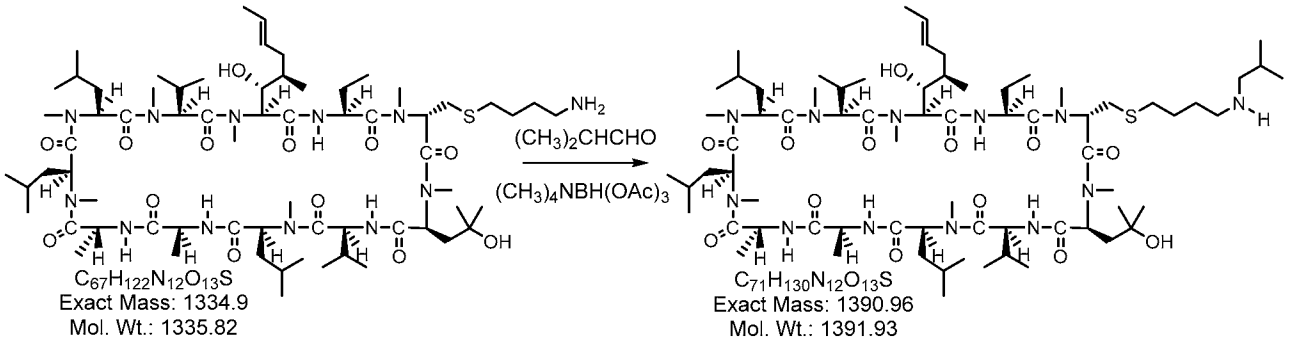
[(S)-(4-(N-Isopropylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0252] [(S)-(4-Aminobuylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (60 mg, 0.05 mmol) and acetone (100 μl) were dissolved in chloroform (5 ml), followed by adding tetramethylammonium triacetoxyborohydride (29.5 mg, 0.11 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product. [Molecular formula: $C_{70}H_{128}N_{12}O_{13}S$; Exact Mass: 1376.94; MS (m/z): 1377.58 $(M+1)^+$, 1399.79 $(M+Na)^+$; TLC R_f: 0.15 (ethyl acetate/methanol = 5/1); HPLC RT: 11.21 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 85

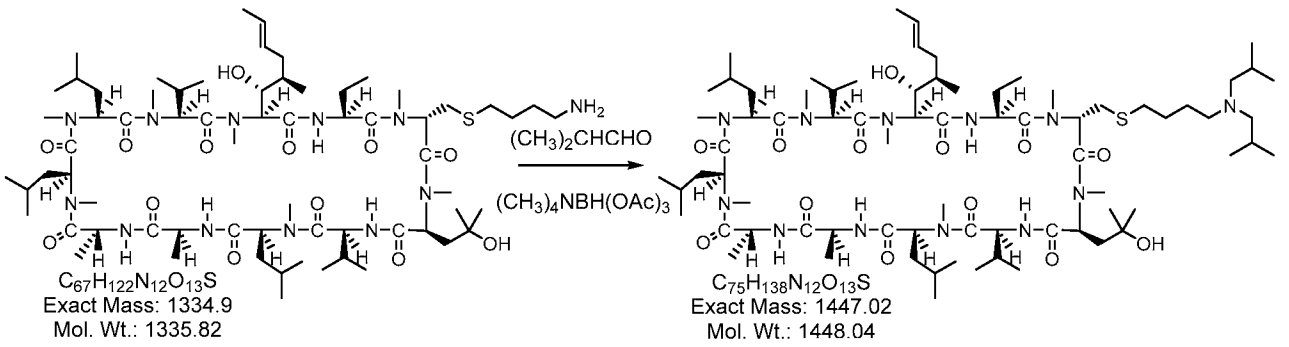
[(S)-(4-(N-Isobutylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0253] [(S)-(4-Aminobuylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (80 mg, 0.060 mmol) and isobutyradehyde (MW 72.11, d 0.794, 27 μl, 0.3 mmol) were dissolved in chloroform (5.0 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (39.4 mg, 0.15 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular formula: $C_{71}H_{130}N_{12}O_{13}S$; Exact Mass: 1390.96; MS (m/z): 1391.58$(M+1)^+$, 1413.74 $(M+Na)^+$; TLC R_f: 0.20 (ethyl acetate/methanol = 5/1); HPLC RT: 11.99 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 86

[(S)-(4-(N,N-Diisobutylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

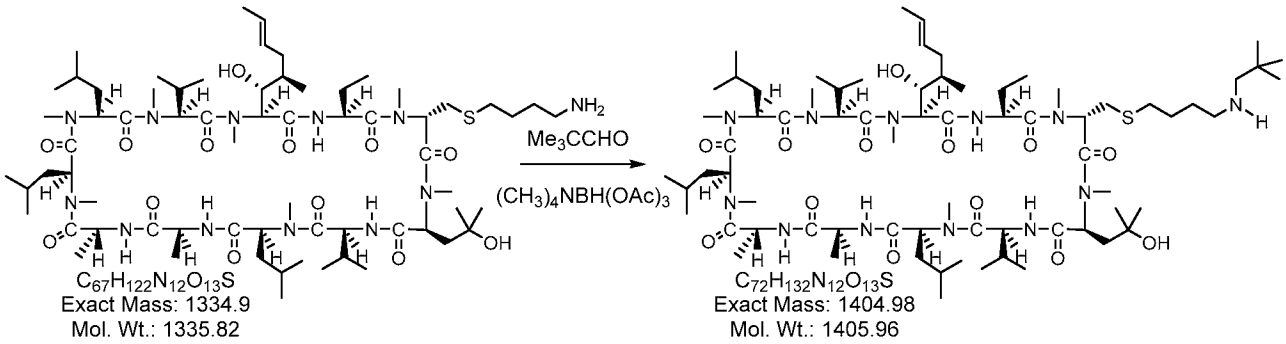


[0254] [(S)-(4-Aminobuylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (80 mg, 0.060 mmol) and isobutyradehyde (MW 72.11, d 0.794, 27 μl, 0.3 mmol) were dissolved in chloroform (5.0 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (39.4 mg, 0.15 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with

saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give product [Molecular formula: $C_{75}H_{138}N_{12}O_{13}S$; Exact Mas: 1447.023; MS (m/z): 1447.63 $(M+1)^+$, 1470.84 $(M+Na)^+$; TLC R_f: 0.25 (ethyl acetate/methanol = 5/1); HPLC RT: 13.84 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 87

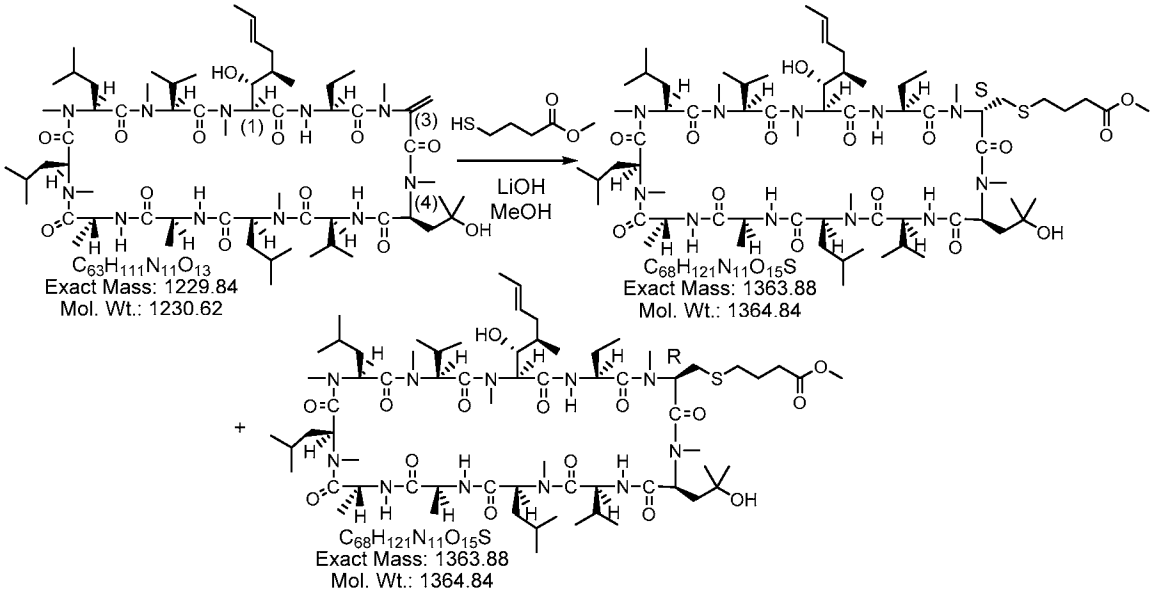
[(S)-(4-(N-Neopentylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0255] [(S)-(4-Aminobuylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (67 mg, 0.05 mmol) and trimethylacetaldehyde (MW 86.13, d 0.781, 27.6 µl, 0.25 mmol) were dissolved in chloroform (5 ml), followed by adding 2.5 equivalents of tetramethylammonium triacetoxyborohydride (32.87 mg, 0.125 mmol). The mixture was stirred at room temperature for two hours. Then the reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using dichloromethane/methanol as eluent to give 25 mg of pure product [Molecular formula: $C_{72}H_{132}N_{12}O_{13}S$; Exact Mass: 1404.98; MS (m/z): 1405.54$(M+1)^+$, 1427.72 $(M+Na)^+$; TLC R_f: 0.17 (ethyl acetate/methanol = 5/1); HPLC RT: 12.66 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 88

[(S)-(3-(Methoxycarbonyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin and [(R)-(3-(methoxycarbonyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

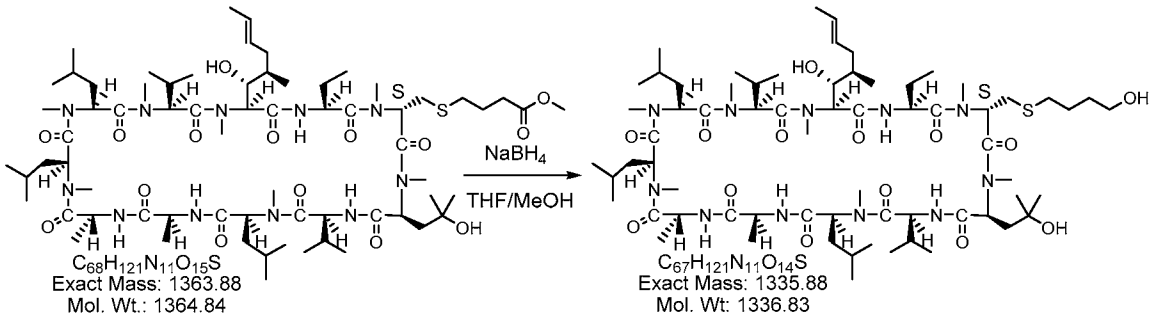


[0256] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (1.28 g, 1.04 mmol) and methyl 4-mercaptobutanoate (0.84 g, 6.24 mmol) in methanol (25 ml) was added lithium hydroxide (0.15 g, 6.24 mmol). The reaction mixture was stirred at room temperature overnight. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and brine (30 ml) were added and the mixture was separated. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone) to give 300 mg of [(S)-(4-(methoxycarbonyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{68}H_{128}N_{11}O_{15}S$; Exact Mass: 1363.88; MS (m/z): 1364.43 $(M+1)^+$, 1386.64 $(M+Na)^+$; HPLC RT: 15.26 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)] and 220 mg of [(R)-(4-(methoxycarbonyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{68}H_{128}N_{11}O_{15}S$; Exact Mass: 1363.88; MS (m/z): 1364.43 $(M+1)^+$, 1386.64 $(M+Na)^+$; HPLC RT: 15.13 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

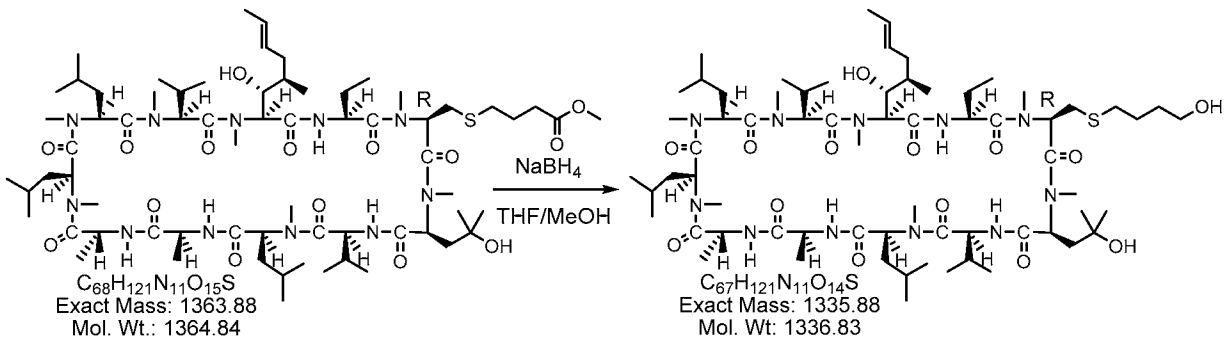
Example 89

[(S)-(4-Hydroxybutylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin and [(R)-(4-hydroxybutylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

Method 1



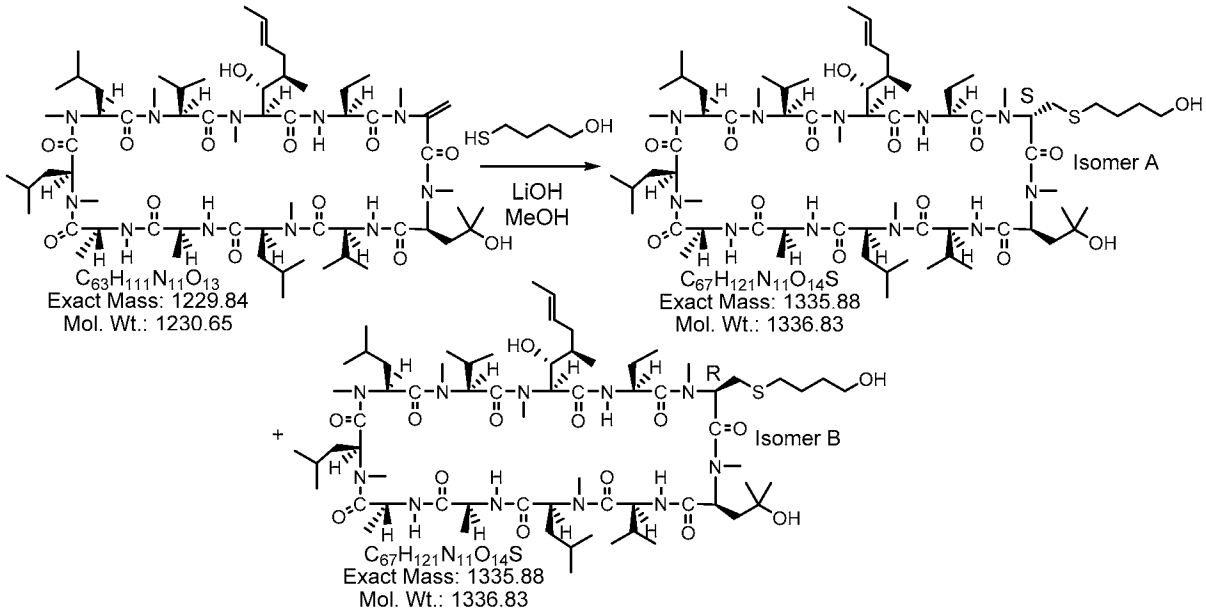
[0257] [(S)-(4-(Methoxycarbonyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (200 mg, 0.15 mmol) was dissolved in tetrahydrofuran (15 ml), followed by adding cesium chloride (200 mg, 1.18 mmol) and sodium borohydride (300 mg, 7.93 mmol). Then 10 ml of methanol was added dropwise to the mixture over 30 minutes. After addition, the mixture was stirred at room temperature one hour. Most solvent was then evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography with dichloromethane/methanol (from 100:0 to 96:4) as eluent to give 13 mg of pure product [Molecular Formula: $C_{67}H_{121}N_{11}O_{14}S$; Exact Mass: 1335.88; MS (m/z): 1336.50 $(M+1)^+$, 1358.70 $(M+Na)^+$; TLC R_f: 0.39 (dichloromethane/methanol = 9:1); HPLC RT: 13.25 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].



[0258] According to this method, 11 mg of pure [(R)-(4-hydroxybutylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin was obtained [Molecular Formula: $C_{67}H_{121}N_{11}O_{14}S$; Exact Mass: 1335.88; MS (m/z): 1336.50 $(M+1)^+$, 1358.70 $(M+Na)^+$; TLC R_f: 0.39 (dichloromethane/methanol = 9:1); HPLC RT: 13.28 min (C8 reverse phase

column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

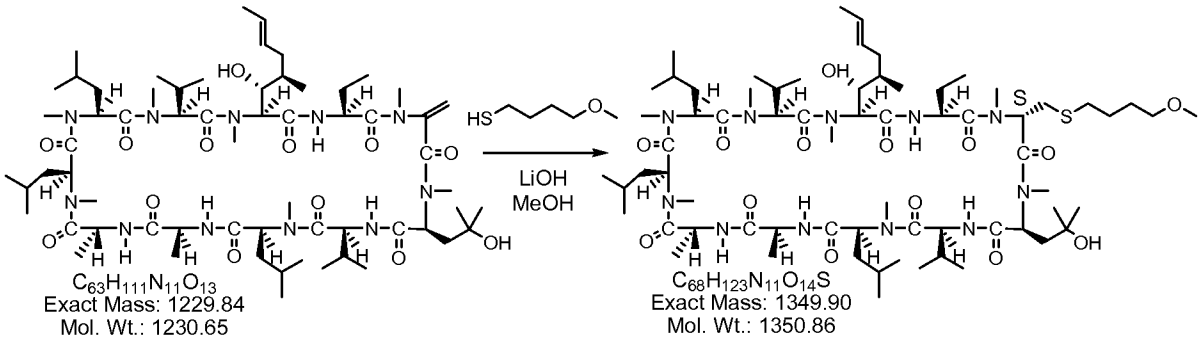
Mehod 2



[0259] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (213 mg, 0.17 mmol) and 4-mercapto-1-butanol (156 mg, 1.44 mmol) in methanol (25 ml) was added lithium hydroxide (94 mg, 3.92 mmol). The reaction mixture was stirred at room temperature overnight. Then most of the solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subject to a flash chromatography using ethyl acetate/methanol as eluent to give product of isomer A as [(S)-(4-hydroxylbutylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin and product of isomer B as [(R)-(4-hydroxylbutylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin [Molecular formula: $C_{67}H_{121}N_{11}O_{14}S$; Exact Mass: 1335.88; MS (m/z): 1336.44 $(M+1)^+$, 1358.67 $(M+Na)^+$; TLC Rf: 0.38 (dichloromethane/methanol = 9/1); TLC Rf (isomer A): 0.25 (ethyl acetate/methanol = 20/1, twice development), and TLC Rf (isomer B): 0.20 (ethyl acetate/methanol = 20/1, twice development); HPLC RT: 13.57 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 90

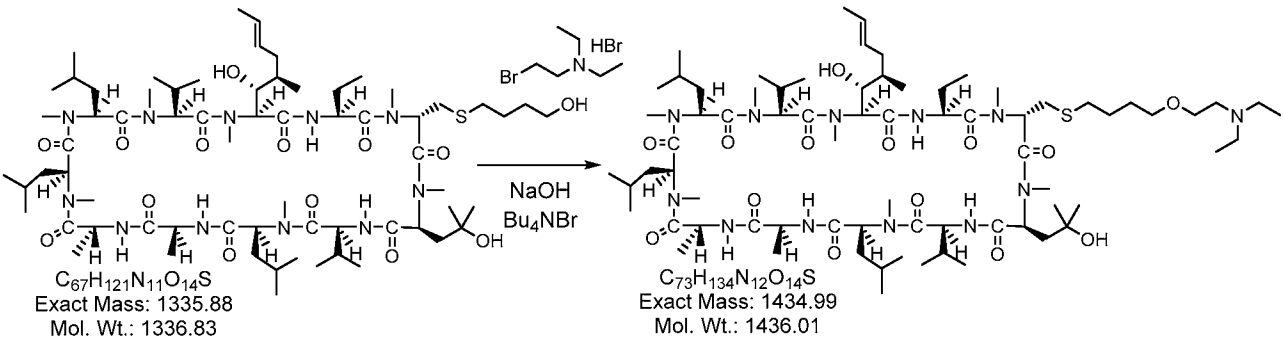
[(S)-(4-Methoxybutylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[0260] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (300 mg, 0.244 mmol) and 1-mercapto-4-methoxybutane (MW: 120.21, 292 mg, 10 mmol) were dissolved in methanol (10 ml), followed by adding six equivalents of lithium hydroxide (35 mg). The mixture was stirred overnight at room temperature. After removal of solvents, the residue was dissolved in ethyl acetate (15 ml). The ethyl acetate solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subject to the flash chromatography using methylene chloride/methanol as eluent to give 57 mg of pure product [Molecular formula: $C_{66}H_{123}N_{11}O_{14}S$; Exact Mass: 1349.90; MS (m/z): 1350.45 $(M+1)^+$, 1372.58 $(M+Na)^+$; TLC R_f: 0.30 (methylene chloride/methanol = 20/1); HPLC RT: 15.54 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 91

[(R)-(4-(2-(N,N-Diethylamino)ethoxy)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

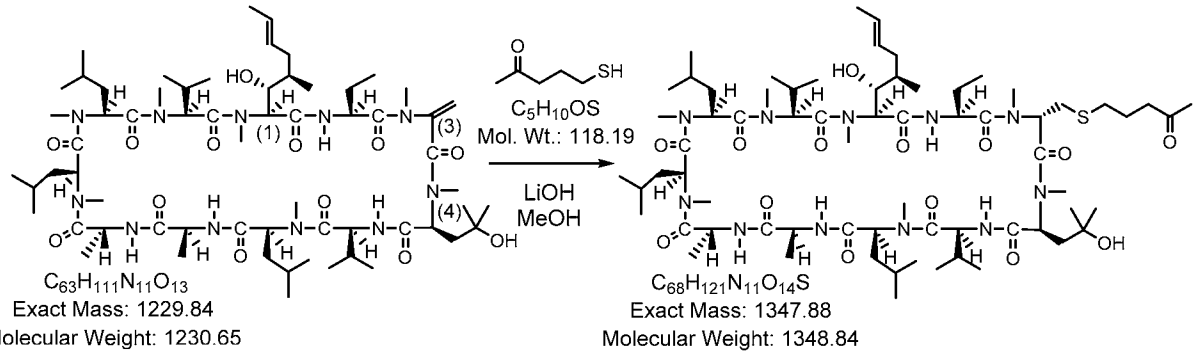


[0261] To a solution of [(R)-(4-hydroxylbutylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.32 g, 0.24 mmol) in benzene (30 ml) were added a solution of sodium hydroxide (1.20 g, 30 mmol) in water (2 ml), 2-bromo-N,N-diethylethylamine hydrobromide (MW: 261, 3.80 g, 14.56 mmol) and tetra-n-butylammonium bromide (0.20 g, 0.62 mmol). The reaction mixture was stirred at 30 °C for 48 hours. After diluted with

ice water, the mixture was separated. The aqueous layer was extracted with dichloromethane (30 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 95/5) to give product [Molecular formula: $C_{73}H_{134}N_{12}O_{14}S$; Exact Mass: 1434.99; MS (m/z): 1435.64$(M+1)^+$; TLC R_f: 0.30 (dichloromethane/methanol = 9/1); HPLC RT: 12.06 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 92

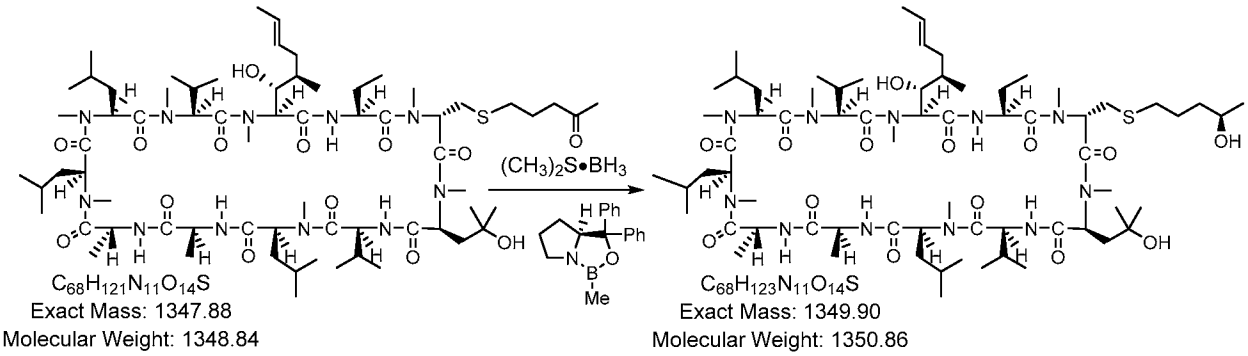
[(S)-((4-Oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (2.00 g, 1.64 mmol) and 5-Mercaptopentan-2-one (1.15 g, 9.73 mmol) in methanol (30 ml) was added lithium hydroxide (233 mg, 9.71 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone from 90/10 to 70/30) to give 400 mg of pure product [Molecular Formula: $C_{68}H_{121}N_{11}O_{14}S$; Exact Mass: 1347.88; MS (m/z): 1348.74 $(M+1)^+$; HPLC RT: 14.72 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 93

[(S)-(((R)-4-Hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

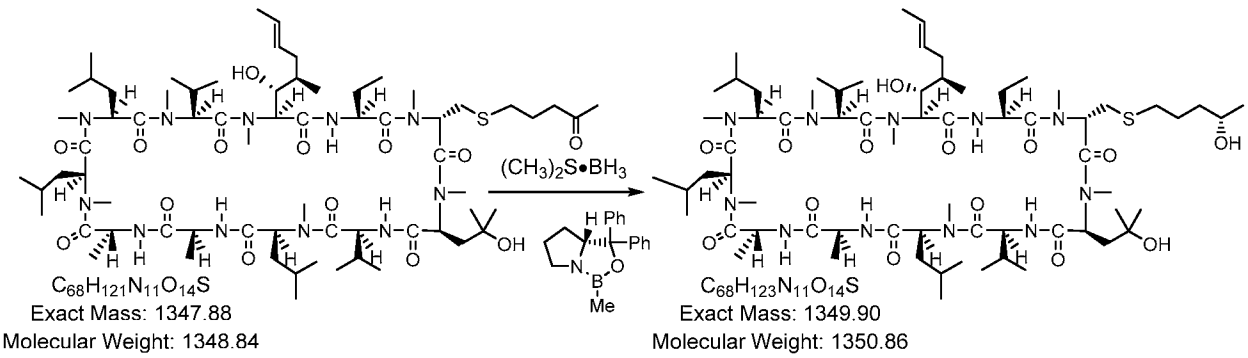


To a solution of [(S)-((4-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

(200 mg, 0.15 mmol) in THF (10 ml) were added (S)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 15 µl, 0.015 mmol) and borane-dimethylsulfide complex (2M in THF, 75 µl, 0.25 mmol) under nitrogen atmosphere. Methanol (5 ml) was added dropwise to the mixture to quench the reaction. The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol from 99/1 to 97/3) to give 18 mg of pure product [Molecular Formula: $C_{68}H_{123}N_{11}O_{14}S$; Exact Mass: 1349.90; MS (m/z): 1350.70 $(M+1)^+$; TLC R_f: 0.74 (dichloromethane/methanol = 9/1); HPLC RT: 14.04 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 94

[(S)-(((S)-4-Hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

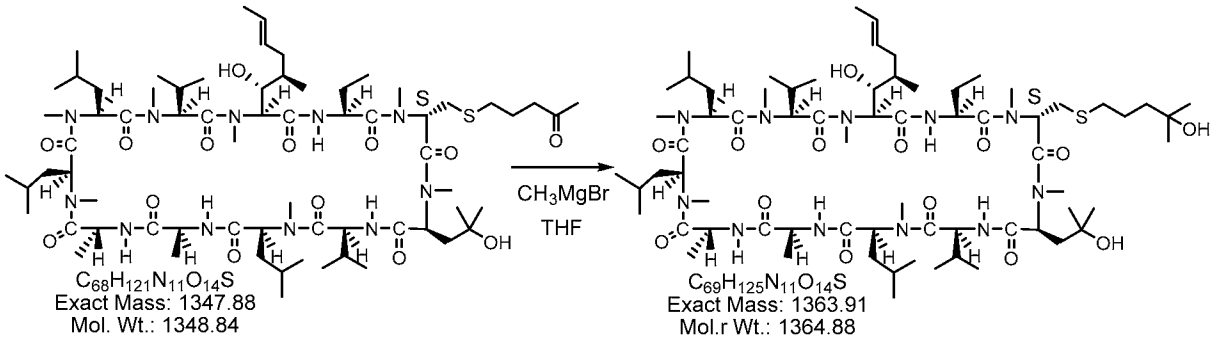


To a solution of [(S)-((4-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

(200 mg, 0.15 mmol) in THF (10 ml) were added (R)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 15 µl, 0.015 mmol) and borane-dimethylsulfide complex (2M in THF, 75 µl, 0.25 mmol) under nitrogen atmosphere. Methanol (5 ml) was added dropwise to the mixture to quench the reaction. The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone from 90/10 to 70/30) to give 33 mg of pure product [Molecular Formula: $C_{68}H_{123}N_{11}O_{14}S$; Exact Mass: 1349.90; MS (m/z): 1350.52 $(M+1)^+$; TLC R_f: 0.74 (dichloromethane/methanol = 9/1); HPLC RT: 13.95 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 95

[(S)-(4-Hydroxy-4-methylpentylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

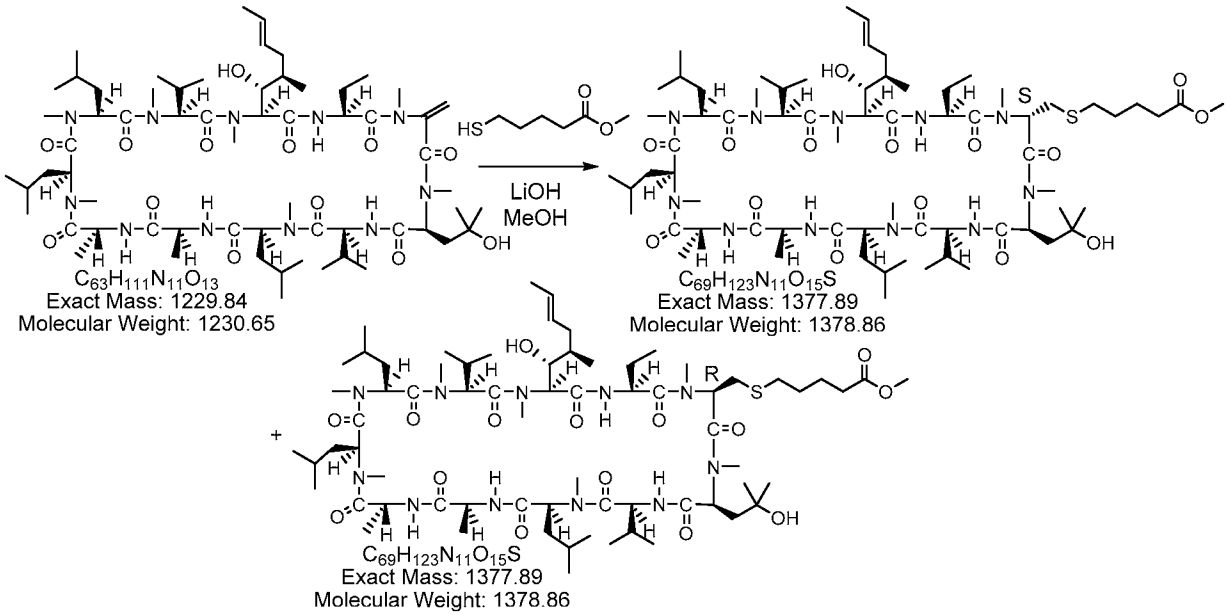


[0262] To a solution of [(S)-4-oxopentylthiomethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (100 mg, 0.07 mmol) in tetrahydrofuran (25 ml) at 0°C was added a solution of methylmagnesium bromide in ether (1 ml, 3 M, 3.00 mmol). After addition, the mixture was slowly warmed to room temperature and stirred at room temperature for one and half hour. Then the reaction was quenched by adding aqueous ammonium chloride solution. Dichloromethane (30 ml) and water (30 ml) were added. The dichloromethane layer was separated and washed with brine (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified on silica gel column with (ethyl acetate/methanol = 99/1) to give a pure product [Molecular formula: $C_{69}H_{125}N_{11}O_{14}S$;

Exact Mass: 1363.91; MS (m/z): 1364.48(M+1)$^+$; TLC Rf: 0.42 (dichloromethane/methanol = 97/3); HPLC RT: 14.74 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 96

[(S)-(4-(Methoxycarbonyl)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin and [(R)-(4-(methoxycarbonyl)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

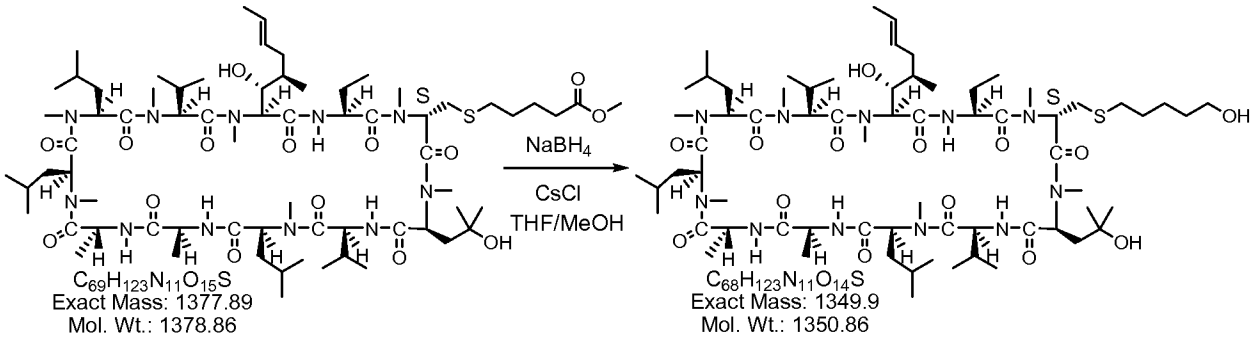


[0209] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (1.00g, 0.81 mmol) and methyl 5-mercaptopentanoate (0.72 g, 4.88 mmol) in methanol (30 ml) was added lithium hydroxide (195 mg, 8.13 mmol). The reaction mixture was stirred at room temperature for 3 hours. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and brine (30 ml) were added and the mixture was separated. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone) to give 210 mg of [(S)-(4-(methoxycarbonyl)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{69}H_{123}N_{11}O_{15}S$; Exact Mass: 1377.89; MS (m/z): 1378.49 (M+1)$^+$, 1400.67 (M+Na)$^+$; HPLC RT: 15.72 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)] and 270 mg of [(R)-(4-(methoxycarbonyl)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{69}H_{123}N_{11}O_{15}S$; Exact Mass: 1377.89; MS (m/z): 1378.50 (M+1)$^+$, 1400.68 (M+Na)$^+$; HPLC RT: 15.53 min (C8 reverse phase column: 250 mm;

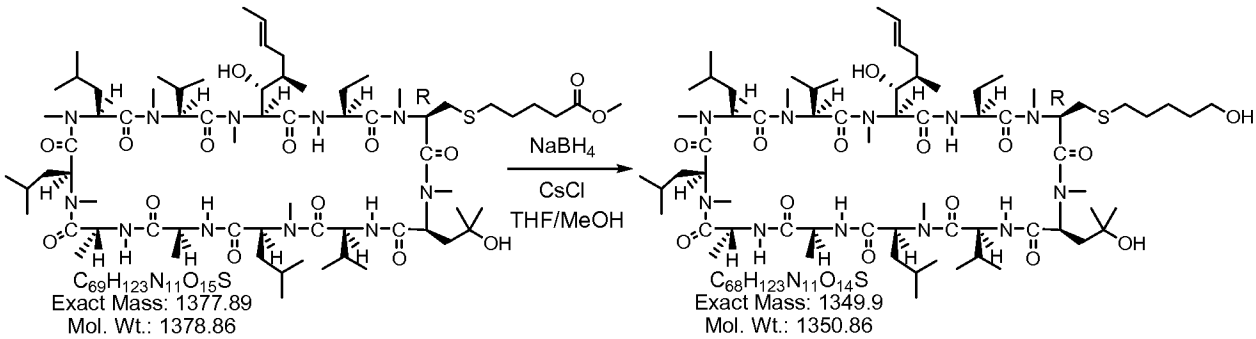
acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 97

[(S)-(5-Hydroxypentylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin and [(R)-(5-Hydroxypentylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



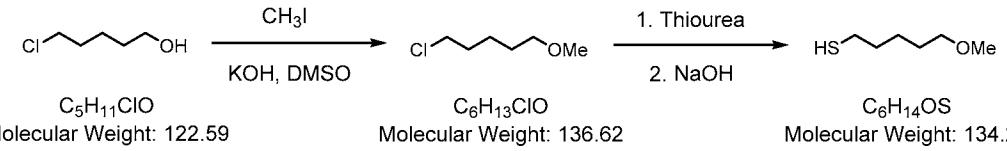
[0263] [(S)-(4-(Methoxycarbonyl)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (170 mg, 0.13 mmol) was dissolved in tetrahydrofuran (30 ml), followed by adding cesium chloride (1.00 g, 5.94 mmol) and sodium borohydride (1.00 g, 26.43 mmol). Then 30 ml of methanol was added dropwise to the mixture over 30 minutes. After addition, the mixture was stirred at room temperature one hour. Most solvent was then evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography with dichloromethane/methanol (from 100:0 to 96:4) as eluent to give 47 mg of pure product of [(S)-(5-hydroxypentylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin [Molecular Formula: $C_{68}H_{123}N_{11}O_{14}S$; Exact Mass: 1349.90; MS (m/z): 1350.52 $(M+1)^+$, 1372.72 $(M+Na)^+$; TLC R_f: 0.54 (dichloromethane/methanol = 9:1); HPLC RT: 14.19 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].



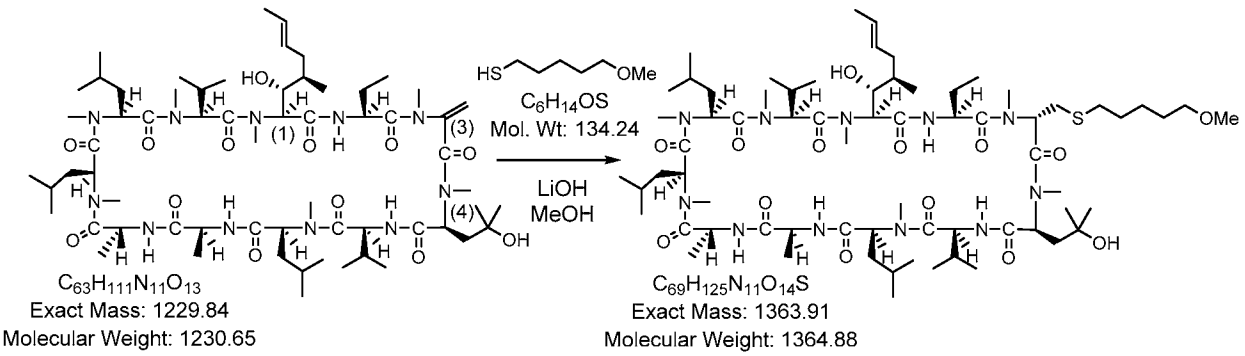
[0264] According to above method, 48 mg of pure [(R)-(5-hydroxypentylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin was obtained [Molecular Formula: $C_{68}H_{123}N_{11}O_{14}S$; Exact Mass: 1349.90; MS (m/z): 1350.47 $(M+1)^+$, 1372.71 $(M+Na)^+$; TLC R_f: 0.54 (dichloromethane/methanol = 9:1); HPLC RT: 14.14 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 98

[(S)-((5-Methoxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



To a solution of 5-chloropentanol (10.60 g, 86.47 mmol) and iodomethane (30.68 g, 216.15 mmol) in dimethyl sulfoxide (10 ml) was added potassium hydroxide (12.10 g, 216.15 mmol). The reaction mixture was stirred at room temperature for one hour and evaporated under reduced pressure. The residue was mixed with ethyl acetate (50 ml) and water (50 ml) and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue (9.5 g) was dissolved in methanol (40 ml). Thiourea (7.00 g, 92.11 mmol) was added. The mixture was stirred and heated to reflux for 3 hours. Then sodium hydroxide (5.59 g, 139 .75 mmol) and water (10 ml) were added. The mixture was stirred and heated to reflux for 6 hours. After cooled to room temperature, the mixture was filtered. The filtrate was evaporated under reduced pressure. The resulting 5-methoxypentanethiol was used for addition reactions without purification.

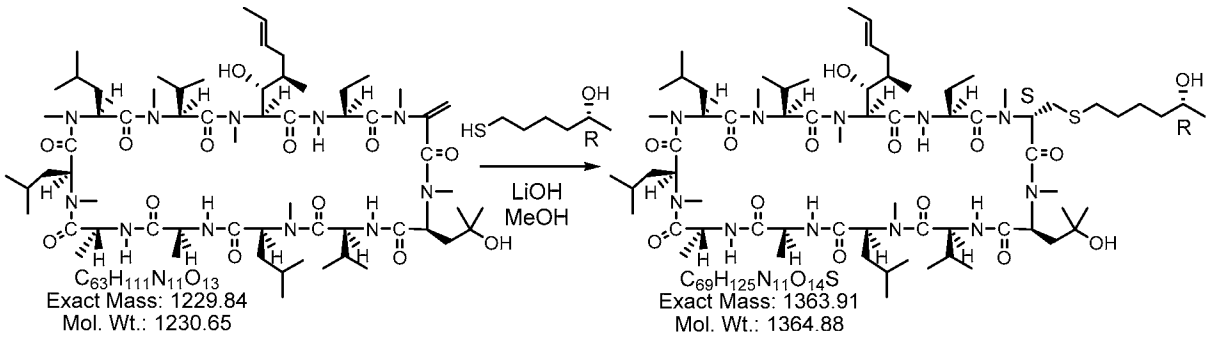


To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (500 mg, 0.41 mmol) and 5-methoxypentanethiol (330 mg, 2.46 mmol) in methanol (15 ml) was added

lithium hydroxide (100 mg, 4.17 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone from 90/10 to 75/25) to give 35 mg of pure product [Molecular Formula: $C_{69}H_{125}N_{11}O_{14}S$; Exact Mass: 1363.91; MS (m/z): 1364.45 $(M+1)^+$; TLC R_f: 0.46 (hexane/acetone = 3/2); HPLC RT: 16.08 min.(C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 99

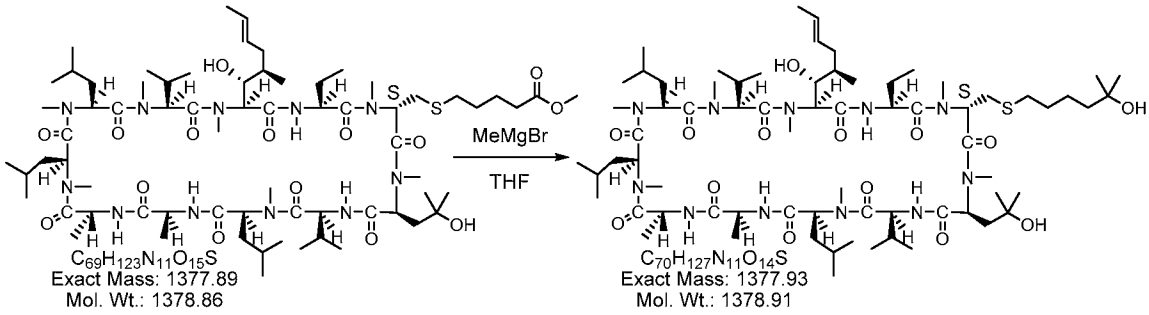
[(S)-((R)-5-Hydroxyhexylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



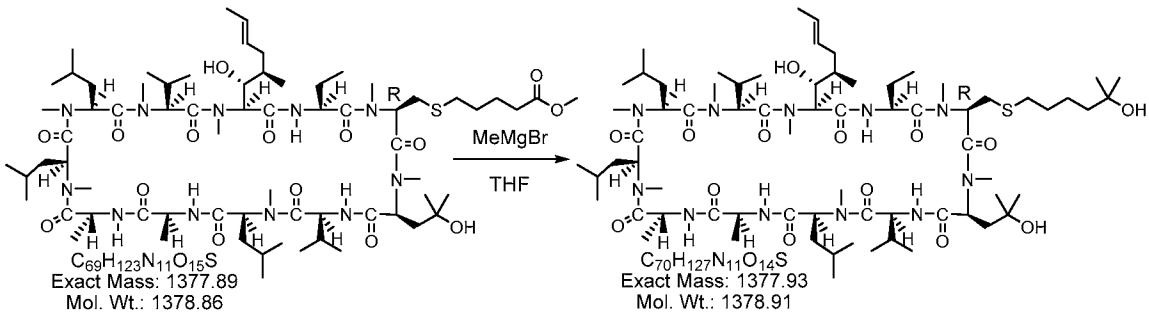
[0265] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (123 mg, 0.1 mmol) and (R)-1-mercapto-5-hexanol (110 mg, 10 mmol) were dissolved in methanol (10 ml), followed by adding 10 equivalents of lithium hydroxide (14.4 mg). The mixture was stirred overnight at room temperature. After removal of solvents, the residue was dissolved in ethyl acetate (15 ml). The ethyl acetate solution was washed with brine, dried over magnesium sulfite and evaporated under reduced pressure. The residue was subject to a flash chromatography using ethyl acetate/methanol as eluent to give 25 mg of pure product [Molecular formula: $C_{69}H_{125}N_{11}O_{14}S$; Exact Mass: 1363.91; MS (m/z): 1364.68 $(M+1)^+$, 1386.87 $(M+Na)^+$; TLC R_f: 0.31 (methylene chloride/methanol = 20/1); HPLC RT: 14.72 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 100

[(S)-((5-Hydroxy-5-methyl)hexylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin and [(R)-((5-Hydroxy-5-methyl)hexylthiothio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



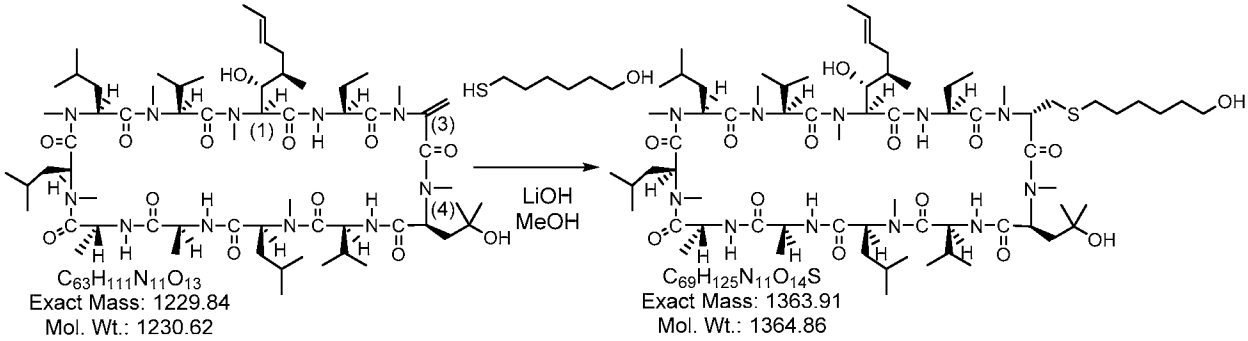
[0266] [(S)-(4-(Methoxycarbonyl)butylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (340 mg, 0.25 mmol) was dissolved in tetrahydrofuran (10 ml) and put into an ice bath. Then 0.63 ml of 3 M methylmagnesium bromide in ether (1.89 mmol) was added dropwise to the mixture over one hour. After the mixture was stirred 0°C for two hour, 3 ml of brine was added dropwise to quench the reaction. Most solvent was then evaporated under reduced pressure. Ethyl acetate (10 ml) and water (10 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography with dichloromethane/methanol as eluent to give 17 mg of pure product [Molecular Formula: $C_{70}H_{127}N_{11}O_{14}S$; Exact Mass: 1377.93; MS (m/z): 1378.55 $(M+1)^+$, 1400.79 $(M+Na)^+$; TLC R_f: 0.48 (dichloromethane/methanol = 9:1); HPLC RT: 15.22 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].



[0267] According to above method, 48 mg of pure [(R)-(5-hydroxy-5-methylhexylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin was obtained [Molecular Formula: $C_{70}H_{127}N_{11}O_{14}S$; Exact Mass: 1377.93; MS (m/z): 1378.45 $(M+1)^+$, 1400.70 $(M+Na)^+$; TLC R_f: 0.41 (dichloromethane/methanol = 9:1); HPLC RT: 15.11 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 101

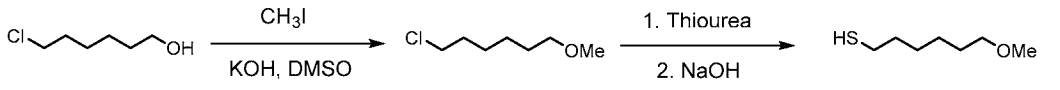
[(S)-(6-Hydroxylhexylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0268] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) and 6-mercapto-1-hexanol (MW: 134.24, 0.27 g, 2.00 mmol) were dissolved in methanol (30 ml), followed by adding 10 equivalents of lithium hydroxide (48 mg, 2.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvents, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subject to the flash chromatography using ethyl acetate/methanol as eluent to give 58 mg of product. [Molecular formula: $C_{69}H_{125}N_{11}O_{14}S$; Exact Mass: 1363.91; MS (m/z): 1364.59 $(M+1)^+$, 1386.76 $(M+Na)^+$; TLC R_f: 0.28 (ethyl acetate/methanol = 20/1); HPLC RT: 14.84 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05 % trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

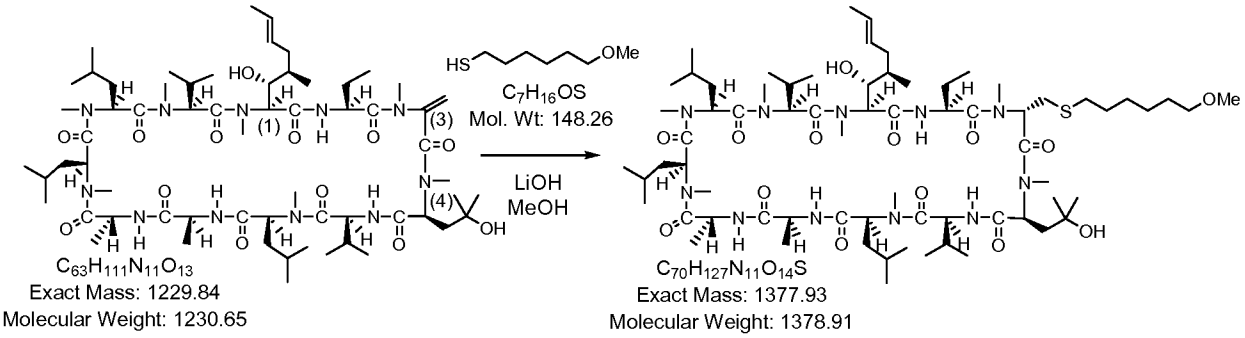
Example 102

[(S)-((6-Methoxyhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



To a solution of 6-chloro-1-hexanol (10.27 g, 75.17 mmol) and iodomethane (26.67 g, 187.90 mmol) in dimethyl sulfoxide (10 ml) was added potassium hydroxide (10.52 g, 187.90 mmol). The reaction mixture was stirred at room temperature for one hour and evaporated under reduced pressure. The residue was mixed with ethyl acetate (50 ml) and water (50 ml) and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue (9.2 g) was dissolved in methanol (40 ml). Thiourea (7.54 g, 99.21 mmol) was added. The mixture was stirred and heated to reflux for 3 hours. Then sodium hydroxide (6.00 g, 150.00 mmol) and water (10 ml) were added. The mixture was stirred and heated to reflux for 6 hours.

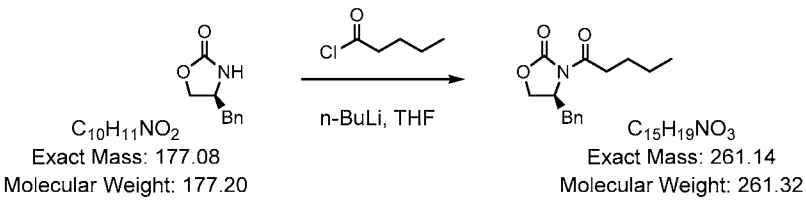
After cooled to room temperature, the mixture was filtered. The filtrate was evaporated under reduced pressure. The resulting 6-methoxyhexanethiol was used for addition reaction without purification.



To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (500 mg, 0.41 mmol) and 6-methoxyhexanethiol (360 mg, 2.43 mmol) in methanol (15 ml) was added lithium hydroxide (100 mg, 4.17 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone from 90/10 to 75/25) to give 29 mg of pure product [Molecular Formula: $C_{70}H_{127}N_{11}O_{14}S$; Exact Mass: 1377.93; MS (m/z): 1378.44 $(M+1)^+$; TLC R_f: 0.49 (hexane/acetone = 3/2); HPLC RT: 16.67 min.(C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

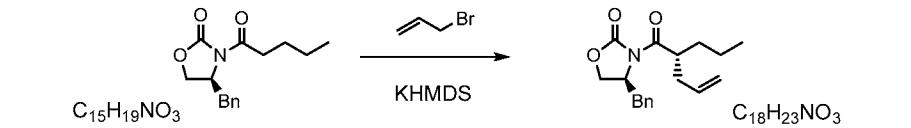
Example 103

Ethyl (R)-2-(2-mercaptoethyl)valerate



To a solution of (S)-4-benzyl-2-oxazolidinone (21.24 g, 0.12 mol) in anhydrous tetrahydrofuran (250 ml) was added n-butyllithium (2.89 M in THF, 44 ml, 0.13 mol) dropwise at -78 °C under nitrogen atmosphere. Then n-valeryl chloride (16.60 g, 0.14 mol) was added over 3 minutes. The mixture was stirred at -78 °C for another hour and warmed to room temperature over 30 minutes. The reaction was quenched with aq. ammonium

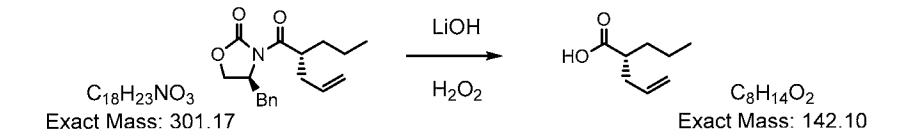
chloride (70 ml) at 0 °C. Tetrahydrofuran was evaporated under reduced pressure. The residue was extracted with dichloromethane (100 ml × 2). The combined dichloromethane layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane to give 29.00 g of pure product (Jeremiah P. Freeman, Editor-in-Chief; submitted by James R. Gage and David A. Evans; checked by Donald T. DeRussy and Leo A. Paquette, 1993, Org. Synth., Coll. Vol. 8, 339, wich is incorporated herein by reference).



$C_{15}H_{19}NO_3$
Exact Mass: 261.14
Molecular Weight: 261.32

$C_{18}H_{23}NO_3$
Exact Mass: 301.17
Molecular Weight: 301.39

To a solution of (S)-3-(1-oxavaleryl)-4-benzyl-2-oxazolidinone (26.10 g, 0.10 mol) in anhydrous tetrahydrofuran (200 ml) was added sodium hexamethyldisilazane (2.0 M in THF, 55 ml, 0.11 mol) dropwise at -78 °C under nitrogen atmosphere. The mixture was stirred at -78 °C for another hour and then ally bromide (42.65 g, 0.35 mol) was added over 5 minutes. After the mixture was stirred at -78 °C for 5 hours, the reaction was quenched with aq. ammonium chloride (90 ml) at -78 °C. Tetrahydrofuran was evaporated under reduced pressure. The residue was extracted with dichloromethane (100 ml × 2). The combined dichloromethane layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane/hexane = 5/1 to give 20.00 g of pure product. [Molecular Formula: $C_{18}H_{23}NO_3$; Exact Mass: 301.17; MS (m/z): 301.98 $(M+1)^+$] (D. A. Evans, M. D. Ennis, D. J. Mathre, 1982, J. Am. Chem. Soc., 104, 1737; S. S. C. Koch, A. R. Chamberlin, 1993, J. Org. Chem. 58, 2725, each of wich is incorporated herein by reference).

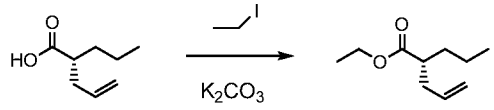


$C_{18}H_{23}NO_3$
Exact Mass: 301.17
Molecular Weight: 301.39

$C_8H_{14}O_2$
Exact Mass: 142.10
Molecular Weight: 142.20

(S)-3-((R)-2-ally-1-oxavaleryl)-4-benzyl-2-oxazolidinone (20.00 g, 66.40 mmol) was dissolved in the mixture solvents of tetrahydrofuran and water (THF/H_2O = 180 ml/60 ml). The flask was sealed with rubber septum, purged with nitrogen and cooled to 0 °C. To this

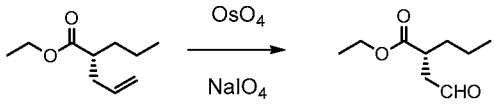
reaction mixture was added H_2O_2 (aq. 35%, 35 ml) over 10 minutes, followed by lithium hydroxide (2.40 g, 0.10 mol) in water (120 ml) solution. The mixture was stirred at 0 °C for 2 hours and sodium sulfite (39 g, 0.31 mol) in water (150 ml) solution was added. Tetrahydrofuran was removed under reduced pressure. The aqueous residue was extracted with dichloromethane (150 ml × 3) to remove (S)-4-benzyl-2-oxazolidinone. Then the aqueous layer was cooled under ice-bath and acidified to PH=1 with 6 M HCl. The mixture was extracted with ethyl acetate (150 ml × 4). The combined ethyl acetate layers were dried over magnesium sulfate and evaporated under reduced pressure to give a crude product 7.00 g.



$C_8H_{14}O_2$
Exact Mass: 142.10
Molecular Weight: 142.20

$C_{10}H_{18}O_2$
Exact Mass: 170.13
Molecular Weight: 170.25

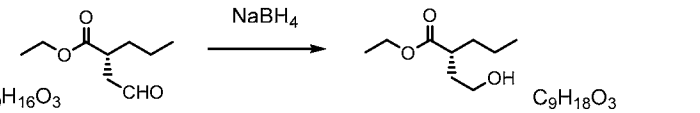
To a solution of (R)-2-ally-valeric acid (7.00 g, 0.05 mol) in N,N-dimethylformamide (80 ml) were added iodoethane (15.60 g, 0.10 mol) and potassium carbonate (13.85 g, 0.10 mol). The mixture was stirred at room temperature for 5 hours. Then 250 ml of ethyl acetate and 100 ml of ice water were added and the mixture was separated. The ethyl acetate layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 7.10 g of crude product.



$C_{10}H_{18}O_2$
Exact Mass: 170.13
Molecular Weight: 170.25

$C_9H_{16}O_3$
Exact Mass: 172.11
Molecular Weight: 172.22

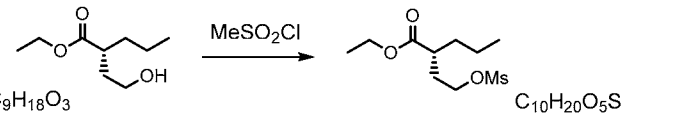
To a solution of ethyl (R)-2-allylvalerate (6.30 g, 37.06 mmol) in the mixture solvents of tetrahydrofuran and water (THF/H_2O = 220 ml/100 ml) was added sodium metaperiodate (27.20 g, 127.16 mmol). Then osmium oxide (4% aq., 10 ml) was added dropwise over 5 minutes. After stirred at room temperature for 5 hours, the mixture was diluted with ethyl acetate (200 ml) and filtered. The ethyl acetate layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 4.00 g of crude product, which was purified on silica gel column with dichloromethane to give 3.50 g of pure product. [Molecular Formula: $C_9H_{16}O_3$; Exact Mass: 172.11; MS (m/z): 172.78 $(M+1)^+$].



$C_9H_{16}O_3$
Exact Mass: 172.11
Molecular Weight: 172.22

$C_9H_{18}O_3$
Exact Mass: 174.13
Molecular Weight: 174.24

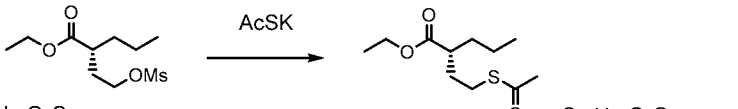
To a solution of ethyl (R)-2-(2-oxoethyl)valerate (3.50 g, 20.34 mmol) in ethanol (80 ml) was added sodium borohydride (1.20 g, 31.55 mmol) in portions at 0 °C. The mixture was stirred at 0 °C for 1 hour. The reaction was quenched with aq. citric acid and PH of the solution was adjusted to 7. Ethanol was removed under reduced pressure. The residue was dissolved in dichloromethane. The dichloromethane layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3.20 g of crude product.



$C_9H_{18}O_3$
Exact Mass: 174.13
Molecular Weight: 174.24

$C_{10}H_{20}O_5S$
Exact Mass: 252.10
Molecular Weight: 252.32

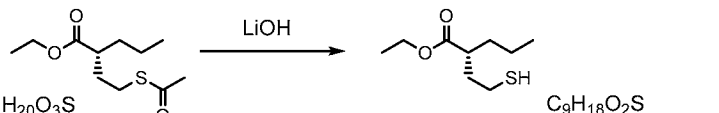
To a solution of ethyl (R)-2-(2-hydroxyethyl)valerate (3.20 g, 18.39 mmol) in anhydrous dichloromethane (80 ml) at 0 °C was added triethylamine (3.05 g, 30.14 mmol), followed by methanesulfonyl chloride (2.40 g, 20.95 mmol). The mixture was stirred at 0 °C for 2 hours. Then the mixture was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 4.10 g of product.



$C_{10}H_{20}O_5S$
Exact Mass: 252.10
Molecular Weight: 252.32

$C_{11}H_{20}O_3S$
Exact Mass: 232.11
Molecular Weight: 232.34

To a solution of ethyl (R)-2-(2-((methylsulfonyl)oxy)ethyl)valerate (4.00 g, 15.86 mmol) in anhydrous N,N-dimethylformamide (30 ml) was added potassium thioacetate (3.45 g, 30.27 mmol). The mixture was stirred and heated to 90 °C for 2.5 hours. After cooled to room temperature, the mixture was diluted with ethyl acetate and water. The oil layer was separated and washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give 2.75 g of product.



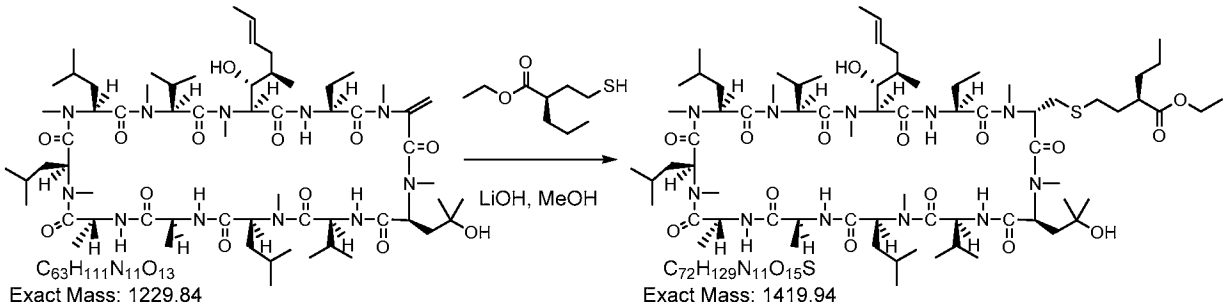
$C_{11}H_{20}O_3S$
Exact Mass: 232.11
Molecular Weight: 232.34

$C_9H_{18}O_2S$
Exact Mass: 190.10
Molecular Weight: 190.30

To a solution of ethyl (R)-2-(2-(acetylthio)ethyl)valerate (2.50 g, 10.77 mmol) in ethanol (30 ml) was added lithium hydroxide (0.30 g, 12.50 mmol). The mixture was stirred at room temperature for 2.5 hours. Ethanol was removed under reduced pressure. The residue was diluted with dichloromethane and water. The PH of aqueous phase was adjusted to 6 with aq. citric acid. The organic phase was separated, dried over magnesium sulfate and evaporated under reduced pressure to give 1.35 g product of ethyl (R)-2-(2-mercaptoethyl)valerate.

Example 104

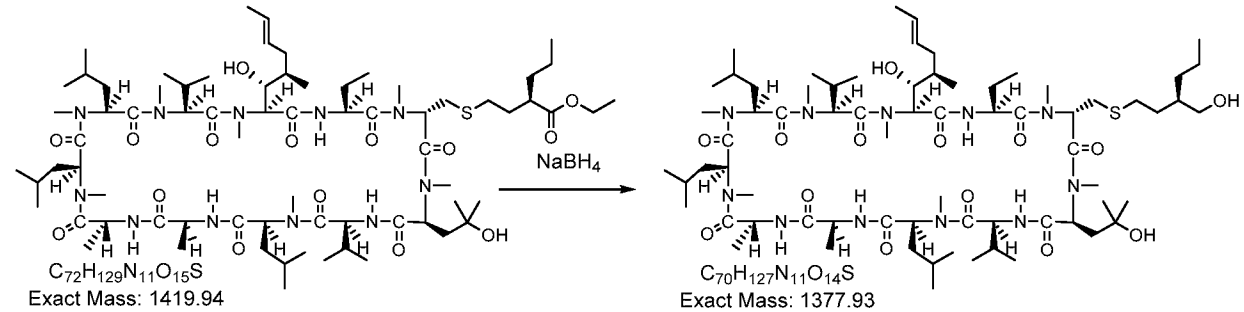
[(S)-((3-(R)-(Ethoxycarbonyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.45 g, 0.37 mmol) and ethyl (R)-2-(2-mercaptoethyl)valerate (0.55 g, 2.90 mmol) were dissolved in methanol (30 ml), followed by adding 8 equivalents of lithium hydroxide. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.20 g of product [Molecular Formula: $C_{72}H_{129}N_{11}O_{15}S$; Exact Mass: 1419.94; MS (m/z): 1420.75 $(M+1)^+$, TLC R_f: 0.55 (ethyl acetate/methanol = 20/1); HPLC RT: 17.48 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 105

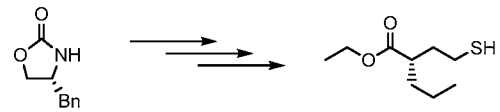
[(S)-((3-(R)-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[(S)-((3-(R)-(Ethoxycarbonyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (270 mg, 0.19 mmol) was dissolved in ethanol (30 ml). Sodium borohydride (1.05 g, 27.61 mmol) was added in portions. After addition, the mixture was stirred at room temperature for 3 days. Most solvent was then evaporated under reduced pressure. Ethyl acetate (50 ml) and water (50 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give the residue, which was purified on silica gel column with dichloromethane/methanol (from 100:0 to 95:5) to give a pure product [Molecular Formula: $C_{70}H_{127}N_{11}O_{14}S$; Exact Mass: 1377.93; MS (m/z): 1378.72 $(M+1)^+$, TLC R_f: 0.35 (ethyl acetate/methanol = 20/1); HPLC RT: 15.72 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 106

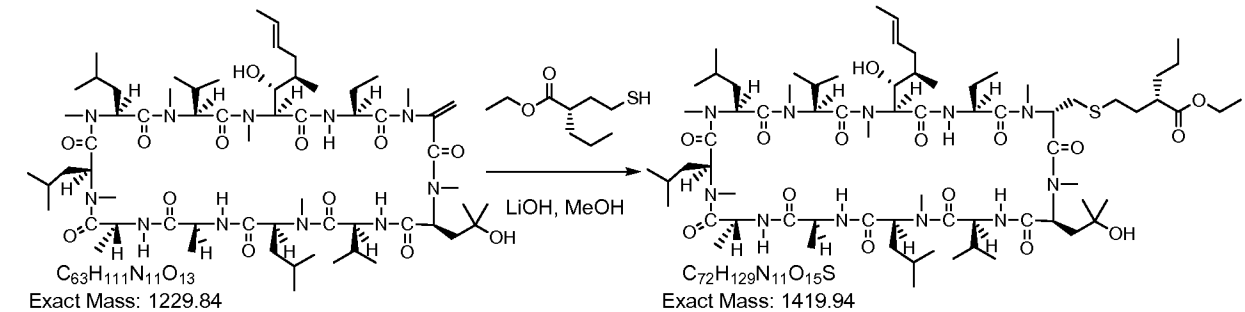
Ethyl (S)-2-(2-mercaptoethyl)valerate



As described as above, ethyl (S)-2-(2-mercaptoethyl)valerate was produced by a similar procedure using (R)-4-benzyl-2-oxazolidinone as starting material via 9 step reactions.

Example 107

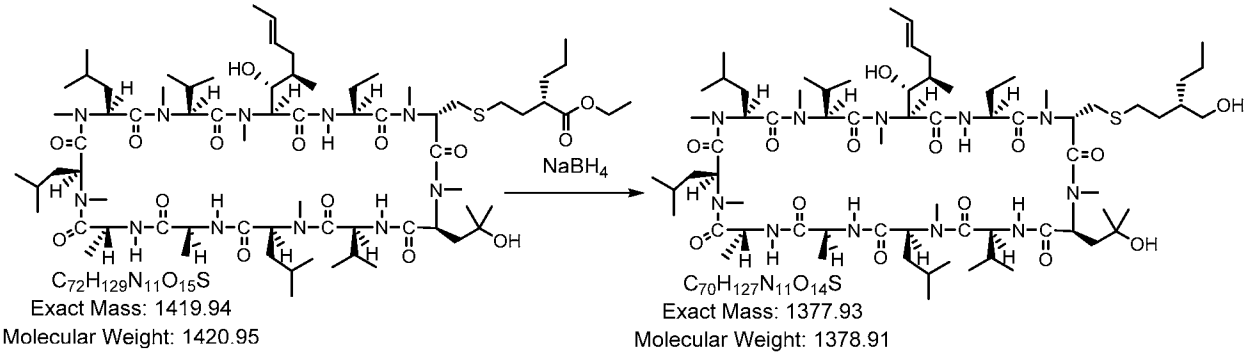
[(S)-((3-(S)-(Ethoxycarbonyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.65 g, 0.53 mmol) and ethyl (S)-2-(2-mercaptoethyl)valerate (0.55 g, 2.90 mmol) were dissolved in methanol (30 ml), followed by adding 8 equivalents of lithium hydroxide. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.20 g of product [Molecular Formula: $C_{72}H_{129}N_{11}O_{15}S$; Exact Mass: 1419.94; MS (m/z): 1420.75 $(M+1)^+$, TLC R_f: 0.55 (ethyl acetate/methanol = 20/1); HPLC RT: 17.51 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 108

[(S)-((3-(S)-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

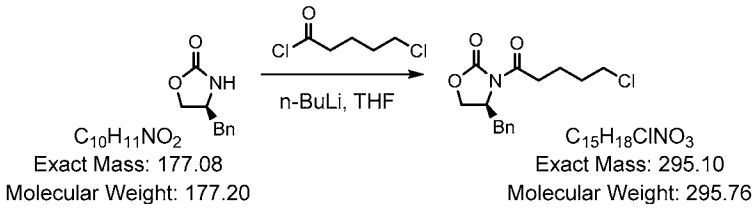


[(S)-((3-(S)-(Ethoxycarbonyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (210 mg, 0.15 mmol) was dissolved in ethanol (30 ml). Sodium borohydride (1.05 g, 27.61 mmol) was added in portions. After addition, the mixture was stirred at room temperature 3 days. Most solvent was then evaporated under reduced pressure. Ethyl acetate (50 ml) and water (50 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give the

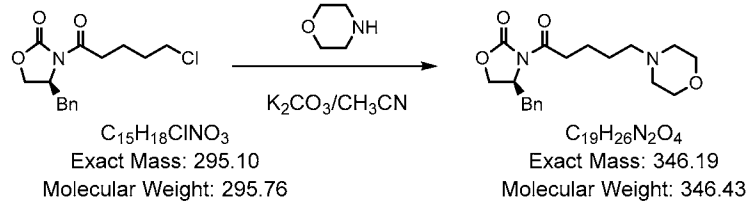
residue, which was purified on silica gel column with dichloromethane/methanol (from 100:0 to 95:5) to give the pure product [Molecular Formula: $C_{70}H_{127}N_{11}O_{14}S$; Exact Mass: 1377.93; MS (m/z): 1378.69 $(M+1)^+$, TLC R_f: 0.35 (ethyl acetate/methanol = 20/1); HPLC RT: 15.71 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 109

Ethyl (R)-2-(2-mercaptoethyl)-5-(4-morpholino)valerate



To a solution of (S)-4-benzyl-2-oxazolidinone (21.24 g. 0.12 mol) in anhydrous tetrahydrofuran (250 ml) was added n-butyllithium (2.89 M in THF, 44 ml, 0.13 mol) dropwise at -78 °C under nitrogen atmosphere, followed by 5-chlorovaleroyl chloride (21.56 g, 0.14 mol) over 3 minutes. The mixture was stirred at -78 °C for another hour and was warmed to room temperature over 30 minutes. The reaction was quenched with aq. ammonium chloride (80 ml) at 0 °C. Tetrahydrofuran was evaporated under reduced pressure. The residue was extracted with dichloromethane (100 ml × 2). The combined dichloromethane layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane to give 16.00 g of pure product.



To a solution of (S)-3-(5-chloro-1-oxavaleryl)-4-benzyl-2-oxazolidinone (16.00 g, 54.22 mmol) in acetonitrile (150 ml) were added morpholine (10.00 g, 114.78 mmol), potassium carbonate (13.82 g, 100.00 mmol) and potassium iodide (8.30 g, 50.00 mmol). The resulting mixture was stirred and heated to reflux for 2 days. After cooled to room temperature, the mixture was filtered and concentrated under reduced pressure. The residue was diluted with dichloromethane and water and separated. The dichloromethane layer was washed with brine,

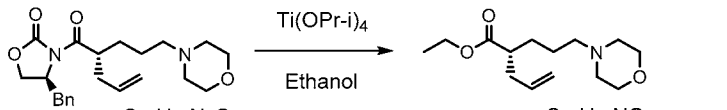
dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane/methanol (100/2) to give 15.00 g of pure product.



$C_{19}H_{26}N_2O_4$
Exact Mass: 346.19
Molecular Weight: 346.43

$C_{22}H_{30}N_2O_4$
Exact Mass: 386.22
Molecular Weight: 386.49

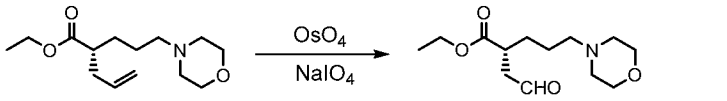
To a solution of (S)-3-(5-(4-morphlinyl)-1-oxavaleryl)-4-benzyl-2-oxazolidinone (15.00 g, 43.33 mmol) in anhydrous tetrahydrofuran (180 ml) was added sodium hexamethyldisilazane (2.0 M in THF, 25 ml, 55 mmol) dropwise at -78 °C under nitrogen atmosphere. The mixture was stirred at -78 °C for another hour. Then ally bromide (21.32 g, 176.20 mmol) was added over 5 minutes. The mixture was stirred at -78 °C for 5 hours. The reaction was quenched with aq. ammonium chloride 90 ml at -78 °C. Tetrahydrofuran was evaporated under reduced pressure. The residue was extracted with dichloromethane (100 ml × 2). The combined dichloromethane layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane/methanol (100/2) to give 13.00 g of pure product. [Molecular Formula: $C_{22}H_{30}N_2O_4$; Exact Mass: 386.22; MS (m/z): 387.17 $(M+1)^+$].



$C_{22}H_{30}N_2O_4$
Exact Mass: 386.22
Molecular Weight: 386.49

$C_{14}H_{25}NO_3$
Exact Mass: 255.18
Molecular Weight: 255.36

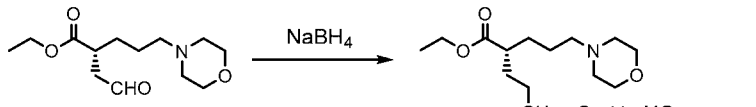
To a solution of (S)-3-(5-(4-morphlinyl)-(R)-2-allyl-1-oxavaleryl)-4-benzyl-2-oxazolidinone (13.00 g, 33.66 mmol) in anhydrous ethanol (150 ml) was added titanium(IV) isopropoxide (19.20 g, 67.55 mmol) under nitrogen atmosphere. The mixture was stirred and heated to reflux overnight. Ethanol was evaporated under reduced pressure. The residue was mixed with dichloromethane (150 ml) and water (100 ml) and separated. The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane/methanol (100/2) to give 7.00 g of product. [Molecular Formula: $C_{14}H_{25}NO_3$; Exact Mass: 255.18; MS (m/z): 256.10 $(M+1)^+$].



$C_{14}H_{25}NO_3$
Exact Mass: 255.18
Molecular Weight: 255.36

$C_{13}H_{23}NO_4$
Exact Mass: 257.16
Molecular Weight: 257.33

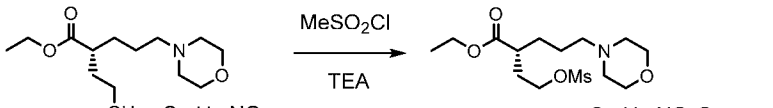
To a solution of ethyl (R)-2-allyl 5-(4-morphlinyl)valerate (7.00 g, 27.43 mmol) in a mixture solvents of tetrahydrofuran and water (THF/H_2O = 240 ml/100 ml) was added sodium metaperiodate (23.20 g, 108.48 mmol). Then osmium oxide (4% aq. 5 ml) was added dropwise over 5 minutes. The mixture was stirred at room temperature for 6 hours, and then diluted with 200 ml of ethyl acetate and filtered. The ethyl acetate layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 4.00 g of crude product, which was purified by on silica gel column with dichloromethane to give 2.00 g of pure product. [Molecular Formula: $C_{13}H_{23}NO_4$; Exact Mass: 257.16; MS (m/z): 258.08 $(M+1)^+$].



$C_{13}H_{23}NO_4$
Exact Mass: 257.16
Molecular Weight: 257.33

$C_{13}H_{25}NO_4$
Exact Mass: 259.18
Molecular Weight: 259.35

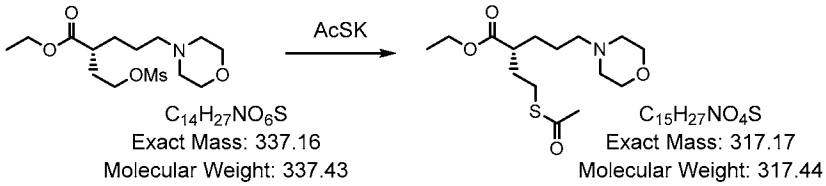
To a solution of ethyl (R)-5-(4-morpholino)-2-(2-oxoethyl)valerate (2.00 g, 7.78 mmol) in ethanol (50 ml) in ice-bath was added sodium borohydride (0.53 g, 13.94 mmol) in portions. The mixture was stirred at 0 °C for 1 hour. The reaction was quenched with aq. citric acid and the PH of the mixture was adjusted to 7. Ethanol was removed under reduced pressure and the residue was extracted with dichloromethane. The dichloromethane layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 1.20 g of crude product.



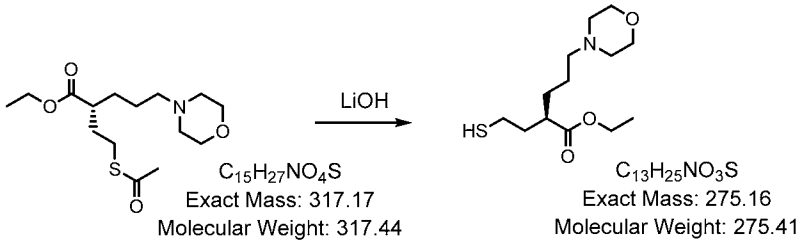
$C_{13}H_{25}NO_4$
Exact Mass: 259.18
Molecular Weight: 259.35

$C_{14}H_{27}NO_6S$
Exact Mass: 337.16
Molecular Weight: 337.43

To a solution of ethyl (R)-2-(2-hydroxyethyl)-5-(4-morpholino)valerate (1.20 g, 4.63 mmol) in anhydrous dichloromethane (30 ml) at 0 °C, was added triethylamine (0.94 g, 9.27 mmol), followed by methanesulfonyl chloride (0.58 g, 5.09 mmol). The mixture was stirred at 0 °C for 2 hours. Then the mixture was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 1.30 g of product.



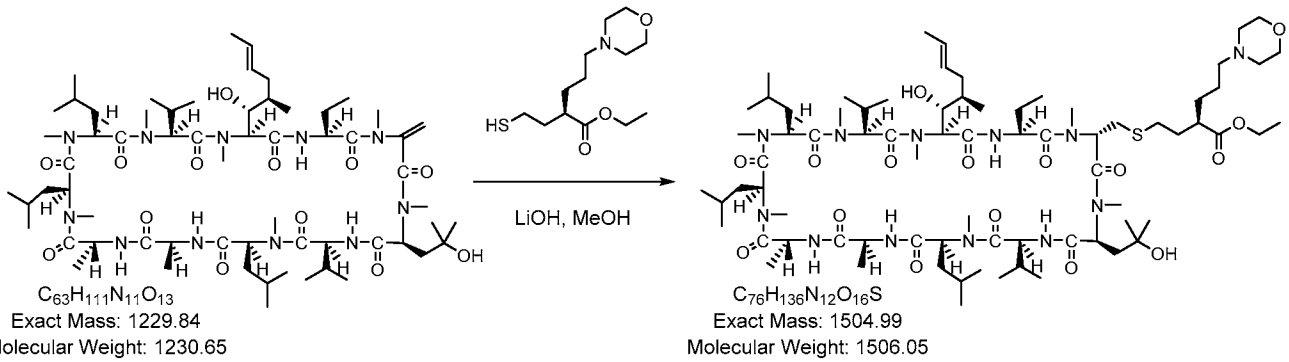
To a solution of ethyl (R)-2-(2-((methylsulfonyl)oxy)ethyl)-5-(4-morpholino)valerate (1.30 g, 3.86 mmol) in anhydrous N,N-dimethylformamide (15 ml) was added potassium thioacetate (0.88 g, 7.72 mmol). The mixture was stirred and heated to 90 °C for 2.5 hours. After cooled to room temperature, the mixture was diluted with ethyl acetate and water. The oil layer was separated, washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give 0.85 g of product.



To a solution of ethyl (R)-2-(2-(acetylthio)ethyl)-5-(4-morpholino)valerate (0.85 g, 2.68 mmol) in ethanol (10 ml) was added lithium hydroxide (0.10 g, 4.16 mmol). The mixture was stirred at room temperature for 2.5 hours. Ethanol was removed under reduced pressure. The residue was diluted with dichloromethane and water. The aqueous phase was adjusted to PH=6 with aq. citric acid. The organic phase was separated, dried over magnesium sulfate and evaporated under reduced pressure to give 0.65 g of product.

Example 110

[(S)-((3-(R)-(Ethoxycarbonyl)-6-(4-morpholino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

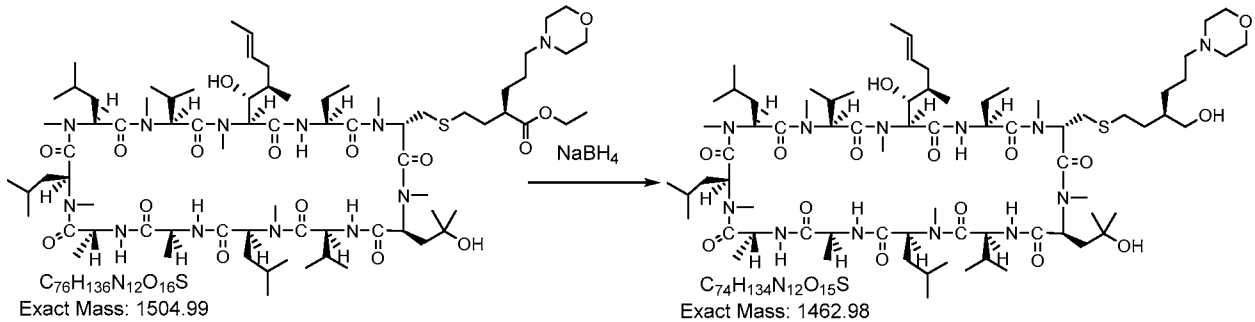


[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.45 g, 0.37 mmol) and ethyl (R)-2-(2-mercaptoethyl)-5-(4-morpholino)valerate (0.65 g, 2.36 mmol) were dissolved in methanol (30 ml), followed by adding 8 equivalents of lithium hydroxide. The mixture was

stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.20 g of product [Molecular Formula: $C_{76}H_{136}N_{12}O_{16}S$; Exact Mass: 1504.99; MS (m/z): 1505.80 $(M+1)^+$, TLC R_f: 0.30 (ethyl acetate/methanol = 20/1); HPLC RT: 11.94 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 111

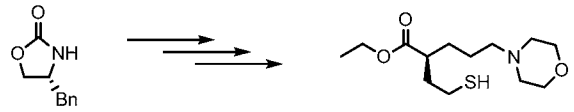
[(S)-((3-(R)-(Hydroxymethyl)-6-(4-morpholino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[(S)-((3-(R)-(Ethoxycarbonyl)-6-(4-morpholino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (210 mg, 0.14 mmol) was dissolved in ethanol (30 ml). Sodium borohydride (1.05 g, 27.61 mmol) was added in portions. After addition, the mixture was stirred at room temperature 3 days. Most solvent was then evaporated under reduced pressure. Ethyl acetate (50 ml) and water (50 ml) were added and separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give the residue, which was purified on silica gel column with dichloromethane/methanol (95:5) to give a pure product [Molecular Formula: $C_{74}H_{134}N_{12}O_{15}S$; Exact Mass: 1462.98; MS (m/z): 1463.79 $(M+1)^+$, TLC R_f: 0.38 (ethyl acetate/methanol = 10/1); HPLC RT: 10.24 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 112

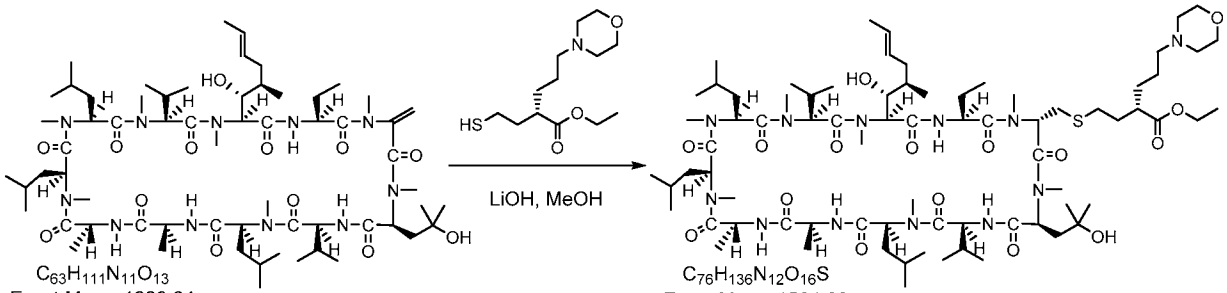
Ethyl (S)-2-(2-mercaptoethyl)-5-(4-morpholino)valerate



As described as above, ethyl (S)-2-(2-mercaptoethyl)-5-(4-morpholino)valerate was produced by a similar procedure using (R)-4-benzyl-2-oxazolidinone as starting material via 9 step reactions.

Example 113

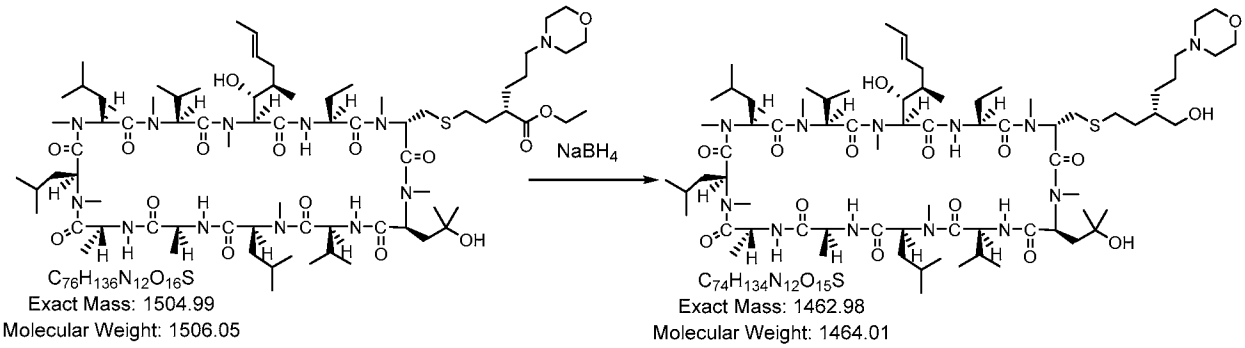
[(S)-((3-(S)-(Ethoxycarbonyl)-6-(4-morpholino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.45 g, 0.37 mmol) and ethyl (S)-2-(2-mercaptoethyl)-5-(4-morpholino)valerate (0.55 g, 2.00 mmol) were dissolved in methanol (30 ml), followed by adding 10 equivalents of lithium hydroxide. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 0.16 g of product [Molecular Formula: $C_{76}H_{136}N_{12}O_{16}S$; Exact Mass: 1504.99; MS (m/z): 1505.73 $(M+1)^+$, TLC R_f: 0.30 (ethyl acetate/methanol = 20/1); HPLC RT: 11.90 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 114

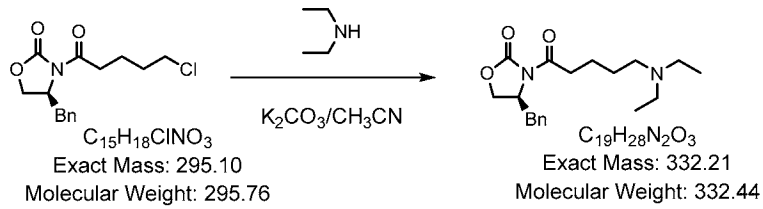
[(S)-((3-(S)-(Hydroxymethyl)-6-(4-morpholino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[(S)-((3-(S)-(Ethoxycarbonyl)-6-(4-morpholino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (160 mg, 0.14 mmol) was dissolved in ethanol (30 ml). Sodium borohydride (0.80 g, 21.04 mmol) was added in portions. After addition, the mixture was stirred at room temperature 3 days. Most solvent was then evaporated under reduced pressure. Ethyl acetate (50 ml) and water (50 ml) were added and separated. The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give the residue, which was purified on silica gel column with dichloromethane/methanol (95:5) to give the pure product [Molecular Formula: $C_{74}H_{134}N_{12}O_{15}S$; Exact Mass: 1462.98; MS (m/z): 1463.73 $(M+1)^+$, TLC R_f: 0.38 (ethyl acetate/methanol = 10/1); HPLC RT: 10.13 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

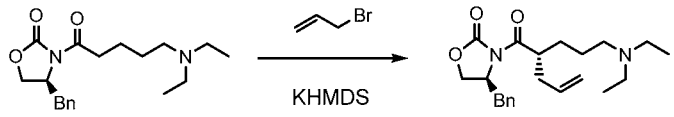
Example 115

(R)-2-(2-Mercaptoethyl)-5-(diethylamino)pentanol



To a solution of (S)-3-(5-chloro-1-oxavaleryl)-4-benzyl-2-oxazolidinone (12.00 g, 40.66 mmol) in acetonitrile (120 ml) were added diethylamine (11.00 g, 150.47 mmol), potassium carbonate (5.56 g, 40.28 mmol) and potassium iodide (8.30 g, 50.00 mmol). The resulting mixture was stirred and heated to reflux for 2 days. After cooled to the room temperature, the mixture was filtered and concentrated under reduced pressure. The residue was diluted with dichloromethane and water and separated. The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product,

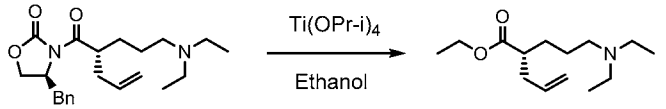
which was purified on silica gel column with dichloromethane/methanol (100/3) to give 12.00 g of pure product.



$C_{19}H_{28}N_2O_3$
Exact Mass: 332.21
Molecular Weight: 332.44

$C_{22}H_{32}N_2O_3$
Exact Mass: 372.24
Molecular Weight: 372.51

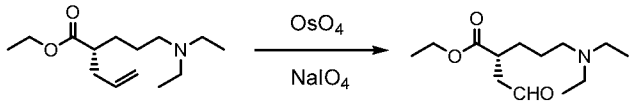
To a solution of (S)-3-(5-diethylamino-1-oxavaleryl)-4-benzyl-2-oxazolidinone (12.00 g, 36.12 mmol) in anhydrous tetrahydrofuran (180 ml) was added sodium hexamethyldisilazane (2.0 M in THF, 19 ml, 38.00 mmol) dropwise at -78 °C under nitrogen atmosphere. The mixture was stirred at -78 °C for another hour. Then ally bromide (16.80 g, 140.05 mmol) was added over 5 minutes. The mixture was stirred at -78 °C for 5 hours. The reaction was quenched with aq. ammonium chloride (90 ml) at -78 °C. Tetrahydrofuran was removed under reduced pressure. The residue was extracted with dichloromethane (100 ml × 2). The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane/methanol (100/3) to give 5.00 g of pure product. [Molecular Formula: $C_{22}H_{32}N_2O_3$; Exact Mass: 372.24; MS (m/z): 373.17 $(M+1)^+$].



$C_{22}H_{32}N_2O_3$
Exact Mass: 372.24
Molecular Weight: 372.51

$C_{14}H_{27}NO_2$
Exact Mass: 241.20
Molecular Weight: 241.38

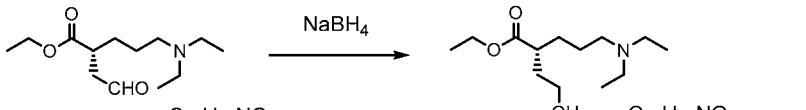
To a solution of (S)-3-((R)-2-allyl-5-diethyamino-1-oxavaleryl)-4-benzyl-2-oxazolidinone (10.00 g, 26.86 mmol) in anhydrous ethanol (180 ml) was added titanium (IV) isopropoxide (19.10 g, 67.20 mmol) under nitrogen atmosphere. The mixture was stirred and heated to reflux overnight. Ethanol was removed under reduced pressure. The residue was mixed with dichloromethane (150 ml) and water (100 ml) and separated. The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a crude product, which was purified on silica gel column with dichloromethane/methanol (100/2) to give 3.00 g of product. [Molecular Formula: $C_{14}H_{27}NO_2$; Exact Mass: 241.20; MS (m/z): 242.02 $(M+1)^+$].



$C_{14}H_{27}NO_2$
Exact Mass: 241.20
Molecular Weight: 241.38

$C_{13}H_{25}NO_3$
Exact Mass: 243.18
Molecular Weight: 243.35

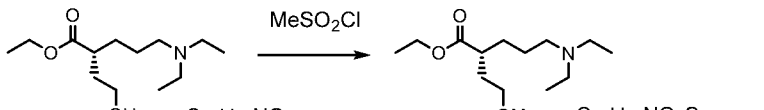
To a solution of ethyl (R)-2-allyl-5-diethylaminovalerate (2.80 g, 11.60 mmol) in a mixture solvents of tetrahydrofuran and water (THF/H_2O = 70 ml/60 ml) was added sodium metaperiodate (9.20 g, 43.02 mmol). Osmium oxide (4% aq. 3 ml) was added dropwise over 5 minutes. The mixture was stirred at room temperature for 2 hours, and then diluted with 100 ml of ethyl acetate and filtered. The ethyl acetate layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 2.15 g of crude product, which was purified by on silica gel column with dichloromethane to give 1.20 g of pure product. [Molecular Formula: $C_{13}H_{25}NO_3$; Exact Mass: 243.18; MS (m/z): 244.05 $(M+1)^+$].



$C_{13}H_{25}NO_3$
Exact Mass: 243.18
Molecular Weight: 243.35

$C_{13}H_{27}NO_3$
Exact Mass: 245.20
Molecular Weight: 245.36

To a solution of ethyl (R)-5-(diethylamino)-2-(2-oxoethyl)valerate (1.20 g, 4.93 mmol) in ethanol (20 ml) in ice-bath was added sodium borohydride (0.38 g, 10.00 mmol) in portions. The mixture was stirred at 0 °C for 1 hour. The reaction was quenched with aq. citric acid and the PH of the mixture was adjusted to 7. Ethanol was removed under reduced pressure. The residue was extracted with dichloromethane. The dichloromethane layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give 1.20 g of crude product.

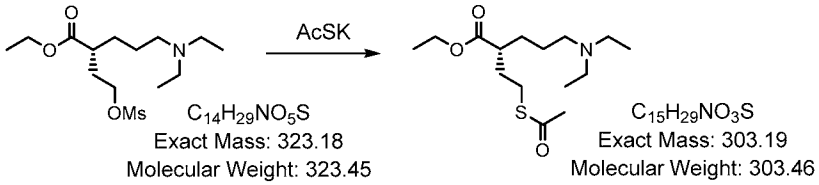


$C_{13}H_{27}NO_3$
Exact Mass: 245.20
Molecular Weight: 245.36

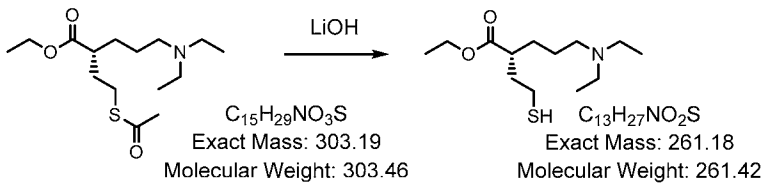
$C_{14}H_{29}NO_5S$
Exact Mass: 323.18
Molecular Weight: 323.45

To a solution of ethyl (R)-2-(2-hydroxyethyl)-5-diethylaminovalerate (1.20 g, 4.89 mmol) in anhydrous dichloromethane (25 ml) at 0 °C was added triethylamine (0.72 g, 7.12 mmol), followed by methanesulfonyl chloride (0.58 g, 5.09 mmol). The mixture was stirred at 0 °C for 2 hours. Then the mixture was washed with water and brine, dried over magnesium

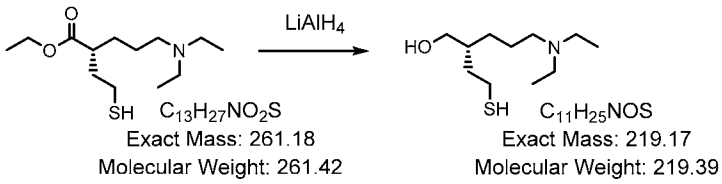
sulfate and evaporated under reduced pressure to give 0.90 g of product. [Molecular Formula: $C_{14}H_{29}NO_5S$; Exact Mass: 323.18; MS (m/z): 323.93 $(M+1)^+$].



To a solution of ethyl (R)-2-(2-((methylsulfonyl)oxy)ethyl)-5-(diethylamino)valerate (0.90 g, 2.78 mmol) in anhydrous N,N-dimethylformamide (15 ml) was added potassium thioacetate (0.70 g, 6.14 mmol). The mixture was stirred and heated to 90 °C for 2.5 hours. After cooled to room temperature, the mixture was mixed with ethyl acetate and water and separated. The oil layer was washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give 0.55 g of product. [Molecular Formula: $C_{15}H_{29}NO_3S$; Exact Mass: 303.19; MS (m/z): 303.99 $(M+1)^+$].



To a solution of ethyl (R)-2-(2-(acetylthio)ethyl)-5-(diethylamino)valerate (0.85 g, 2.80 mmol) in ethanol (10 ml) was added lithium hydroxide (0.10 g, 4.16 mmol). The mixture was stirred at room temperature for 2.5 hours. Ethanol was removed under reduced pressure. The residue was diluted with dichloromethane and water. The aqueous phase was adjusted to PH=6 with aq. citric acid. The organic phase was separated, dried over magnesium sulfate and evaporated under reduced pressure to give 0.60 g of product.

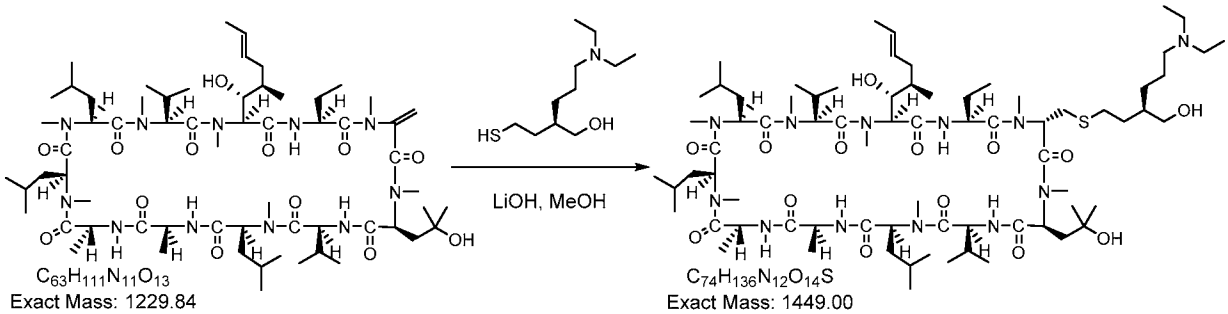


To a solution of ethyl (R)-2-(2-thioethyl)-5-diethylaminovalerate (0.60 g, 2.30 mmol) in anhydrous tetrahydrofuran (50 ml) was added lithium aluminum hydride (1.0 M in ether, 4 ml, 4.00 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at this temperature for 2 hours. Then the mixture was warmed to room temperature, mixed with

ethyl acetate (20 ml) and stirred for another hour. The mixture was filtered and concentrated under reduced pressure to give 0.40 g of product.

Example 116

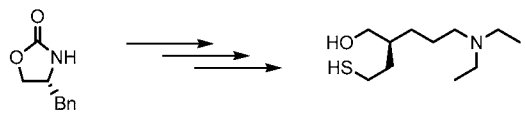
[(S)-((3-(R)-(Hydroxymethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.45 g, 0.37 mmol) and (R)-2-(2-mercaptoethyl)-5-(diethylamino)pentanol (0.40 g, 1.83 mmol) were dissolved in methanol (30 ml), followed by adding 5 equivalents of lithium hydroxide. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a pure product [Molecular Formula: $C_{74}H_{136}N_{12}O_{14}S$; Exact Mass: 1449.00; MS (m/z): 1449.65 $(M+1)^+$, TLC R_f: 0.30 (ethyl acetate/methanol = 10/1); HPLC RT: 12.62 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 117

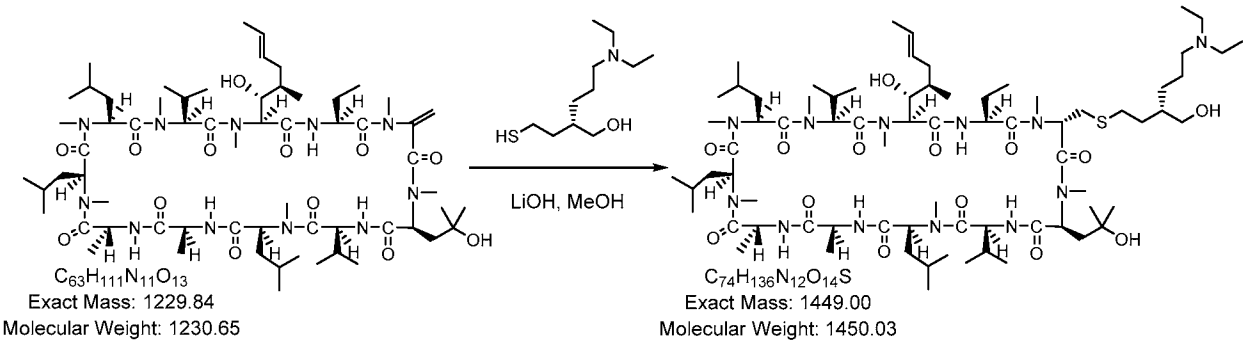
(S)-2-(2-Mercaptoethyl)-5-(diethylamino)pentanol



As described as above, ethyl (S)-2-(2-mercaptoethyl)-5-(diethylamino)pentanol was produced by a similar procedure using (R)-4-benzyl-2-oxazolidinone as starting material via 9 step reactions.

Example 118

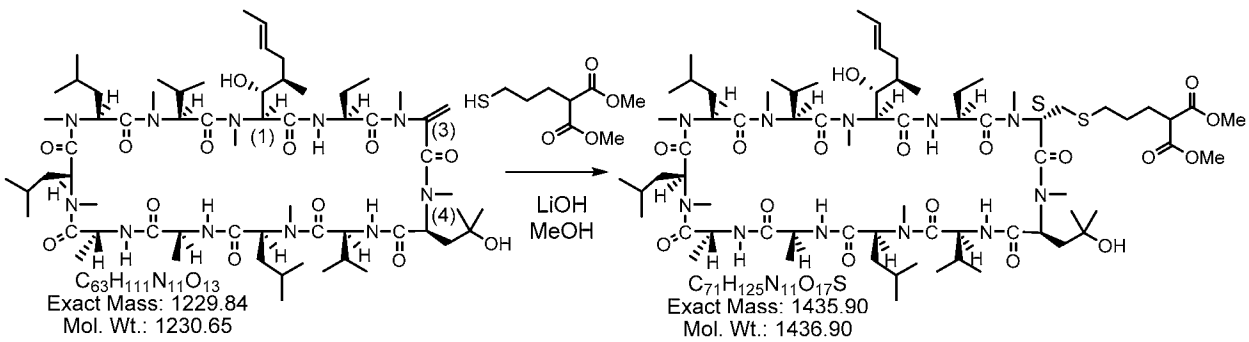
[(S)-((3-(S)-(Hydroxymethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.45 g, 0.37 mmol) and (R)-2-(2-mercaptoethyl)-5-(diethylamino)pentanol (0.40 g, 1.83 mmol) were dissolved in methanol (30 ml), followed by adding 5 equivalents of lithium hydroxide. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a pure product [Molecular Formula: $C_{74}H_{136}N_{12}O_{14}S$; Exact Mass: 1449.00; MS (m/z): 1449.65 $(M+1)^+$, TLC R_f: 0.30 (ethyl acetate/methanol = 10/1); HPLC RT: 12.62 min. (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 119

[(S)-((5-Methoxy-4-methoxycarbonyl)-5-oxopentylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

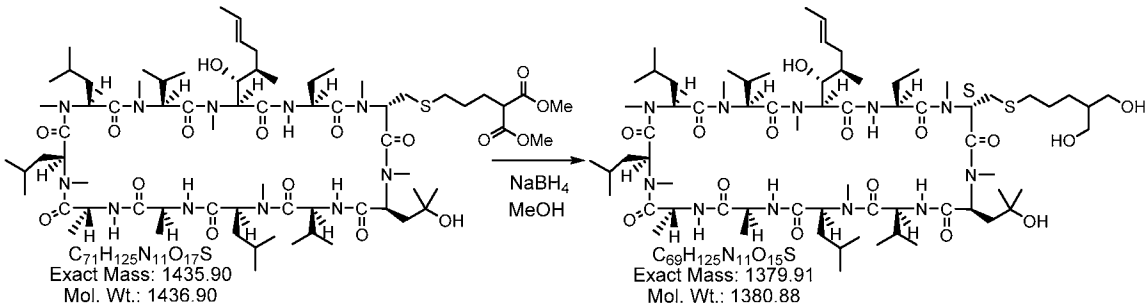


[0269] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (580 mg, 0.47 mmol) and dimethyl 3-mercaptopropylmalonate (MW: 206.26, 600 mg, 2.91 mmol) in methanol (30 ml) was added lithium hydroxide (110 mg, 4.58 mmol). The

reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (100 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was used for next step. [Molecular formula: $C_{71}H_{125}N_{11}O_{17}S$; Exact Mass: 1435.90; MS (m/z): 1436.45 $(M+1)^+$.

Example 120

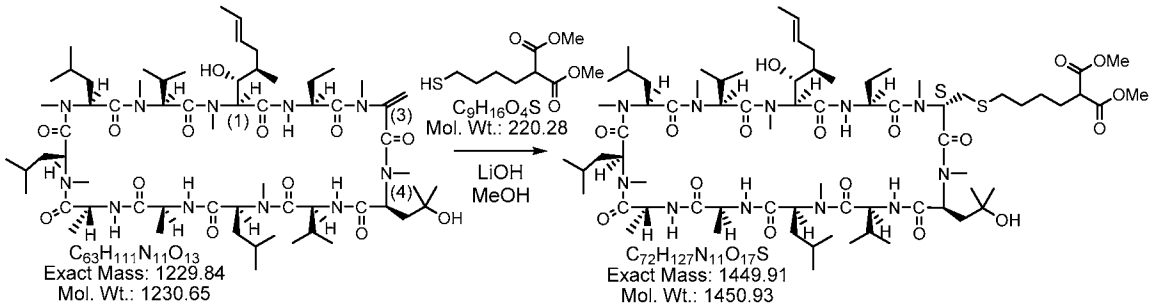
[(S)-((5-Hydroxy-4-hydroxymethyl)pentylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[0270] To a solution of [(S)-((5-methoxy-4-methoxycarbonyl)-5-oxopentylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (280 mg, 0.19 mmol) in methanol (30 ml) was added sodium borohydride (360 mg, 9.52 mmol) in portions. The reaction mixture was stirred at room temperature 3 hours. Then most of the solvent was evaporated under reduced pressure. Dichloromethane (100 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give a pure product [Molecular formula: $C_{69}H_{125}N_{11}O_{15}S$; Exact Mass: 1379.91; MS (m/z): 1380.49 $(M+1)^+$; TLC Rf: 0.23 (dichloromethane/methanol = 95/5); HPLC RT: 12.05 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 121

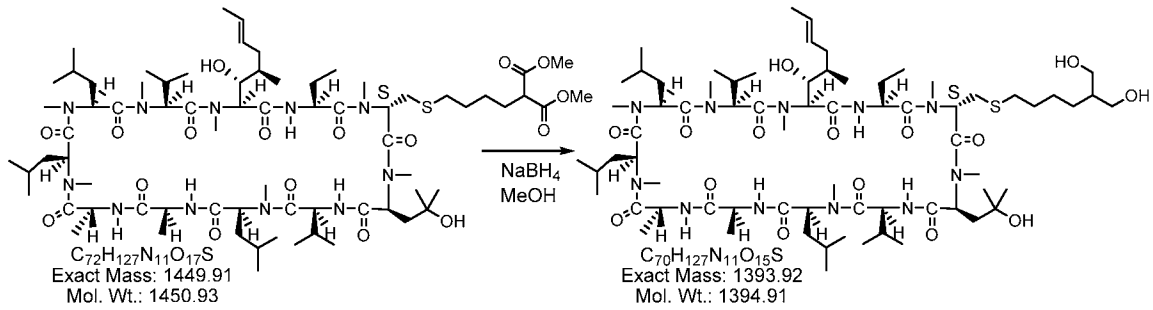
[(S)-(6-Methoxy-(5-methoxycarbonyl)-6-oxohexylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[0271] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (500 mg, 0.41 mmol) and dimethyl 4-mercaptobutylmalonate (650 mg, 2.95 mmol) in methanol (80 ml) was added lithium hydroxide (110 mg, 4.58 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (100 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was used for next step. [Molecular formula: $C_{72}H_{127}N_{11}O_{17}S$; Exact Mass: 1449.91; MS (m/z): 1450.37 $(M+1)^+$.

Example 122

[(S)-(6-Hydroxy-(5-hydroxymethyl)hexylthiomethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

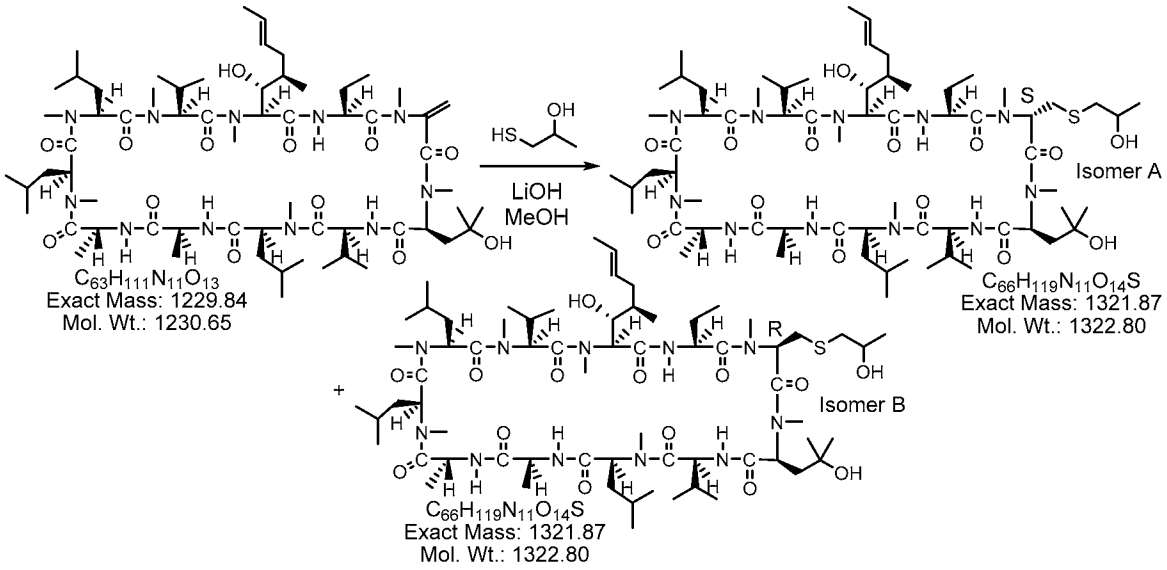


[0272] To a solution of [(S)-(6-methoxy-5-methoxycarbonyl)-6-oxohexylthiomethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.17 mmol) in methanol (40 ml) was added sodium borohydride (350 mg, 9.26 mmol) in portions. The reaction mixture was stirred at room temperature 3 hours. Then most of solvent was evaporated under reduced pressure. Dichloromethane (100 ml) and water (30 ml) were added and separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give a pure product [Molecular formula: $C_{70}H_{127}N_{11}O_{15}S$; Exact Mass: 1393.92; MS (m/z): 1394.45 $(M+1)^+$; TLC Rf: 0.25

(dichloromethane/methanol = 95/5); HPLC RT: 12.62 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 123

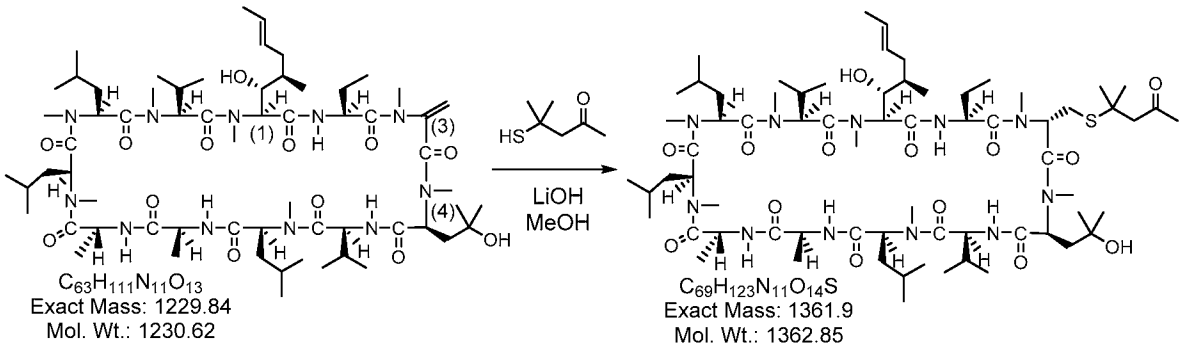
[(S)-(2-Hydroxypropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin and [(R)-(2-Hydroxypropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[0273] [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.246 g, 0.2 mmol) and 1-mercapto-2-propanol (0.184 g, 2 mmol) were dissolved in methanol (10 ml), followed by adding 10 equivalents of lithium hydroxide (48 mg). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in ethyl acetate (15 ml). The ethyl acetate solution was washed with brine, dried over magnesium sulfite and evaporated under reduced pressure. The residue was subject to a flash chromatography using ethyl acetate/methanol as eluent to give the product of isomer A as [(S)-(2-Hydroxypropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin and the product of isomer B as [(R)-(2-Hydroxypropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin [Molecular formula: $C_{66}H_{119}N_{11}O_{14}S$; Exact Mass: 1321.87; MS (m/z): 1322.50 $(M+1)^+$, 1344.76 $(M+Na)^+$; TLC R_f (isomer A): 0.29 (methylene chloride/methanol = 20/1, twice development); TLC R_f (isomer B): 0.26 (methylene chloride/methanol = 20/1, twice development); HPLC RT: 13.62 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 124

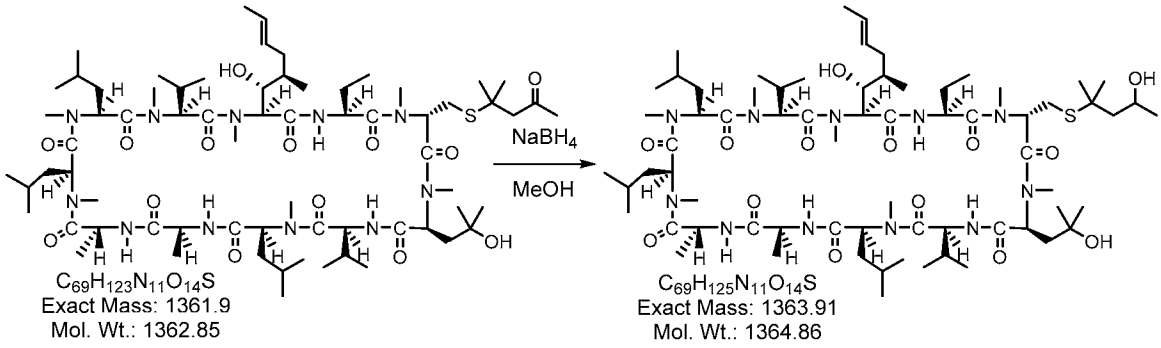
[(S)-(2-Methyl-4-oxypentan-2-ylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0274] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (500 mg, 0.41 mmol) and 4-mercapto-4-methyl-2-pentanone (680 mg, 5.15 mmol) in methanol (25 ml) was added lithium hydroxide (160 mg, 6.66 mmol). The reaction mixture was stirred at room temperature for 3 days. Then most of the solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate) to give the product [Molecular formula: $C_{69}H_{123}N_{11}O_{14}S$; Exact Mass: 1361.90; MS (m/z): 1362.50 $(M+1)^+$; TLC Rf: 0.47 (dichloromethane/methanol = 97/3); HPLC RT: 15.51 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 125

[(S)-(2-Methyl-4-hydroxypentan-2-ylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

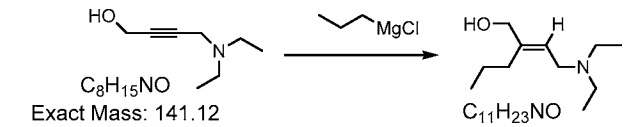


[0275] To a solution of [(S)-(2-methyl-4-oxypentan-2-ylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (68 mg, 0.03 mmol) in methanol (5 ml) were added sodium borohydride (36 mg, 0.95 mmol) in portions. After addition, the mixture was stirred at room

temperature one hour. Most solvent was then evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The dichloromethane layer was washed with brine (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified on silica gel column with dichloromethane/methanol (95/5) as eluent to give the product [Molecular formula: $C_{69}H_{125}N_{11}O_{14}S$; Exact Mass: 1363.91; MS (m/z): 1364.44$(M+1)^+$; TLC Rf: 0.38 (dichloromethane/methanol = 97/3); HPLC RT: 15.03 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 126

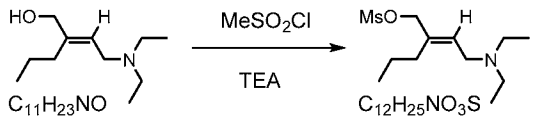
E-4-Diethylamino-2-propyl-2-butene-1-thiol



$C_8H_{15}NO$
Exact Mass: 141.12
Molecular Weight: 141.21

$C_{11}H_{23}NO$
Exact Mass: 185.18
Molecular Weight: 185.31

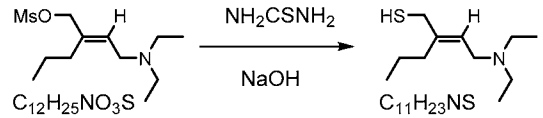
To a solution of n-propylmagnesium chloride 100 ml (1 M in THF) in benzene (100 ml) was added a solution of 4-diethylamino-2-butyn-1-ol (7.0 g , 4.96 mmol) in tetrahydrofuran (30 ml) over 10 min. under nitrogen atmosphere. The resulting mixture was stirred and heated to reflux for 7 hours. After cooled to room temperature, the mixture was quenched with aq. NH_4Cl and filtered. The filtrate was separated. The organic layer washed with dichloromethane and water, dried over magnesium sulfate and evaporated under reduced pressure. The residue was distilled under reduce pressure (110°C/12 mmHg) to give a product (5.2 g).



$C_{11}H_{23}NO$
Exact Mass: 185.18
Molecular Weight: 185.31

$C_{12}H_{25}NO_3S$
Exact Mass: 263.16
Molecular Weight: 263.40

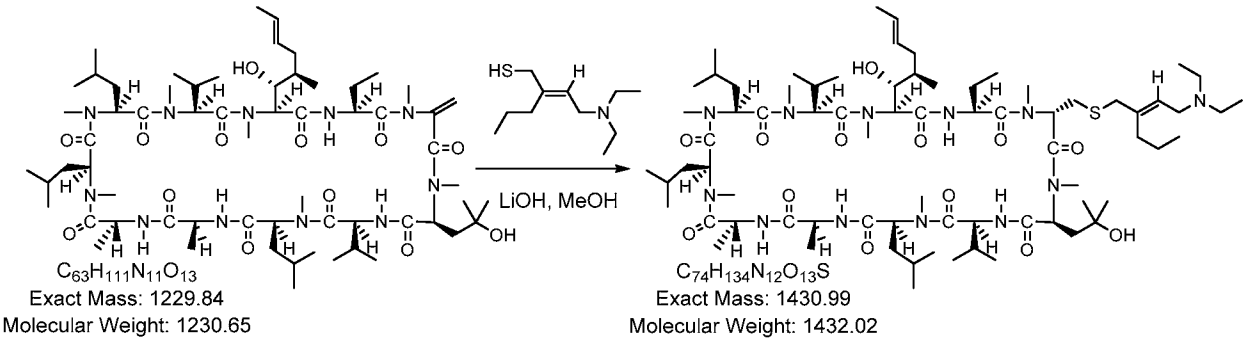
To a solution of E-4-diethylamino-2-propyl-2-buten-1-ol (2.2 g, 11.90 mmol) in dichloromethane (40 ml) in ice-water cooling bath was added triethylamine (1.7 8 g, 17.6 mmol), followed by addition of methanesulfonyl chloride (1.50 g, 13.16 mmol) slowly. The mixture was stirred at 0°C for one hour and then warmed to room temperature over one hour. The dichloromethane solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure to give a product (1.6 g).



To a solution of E-4-diethylamino-2-propyl-1-methylsulfonyloxa-2-buten (1.6 g, 6.08 mmol) in ethanol (50 ml) was added thiourea (1.0 g, 13.2 mmol). The mixture was stirred and heated to reflux for 8 hours, then sodium hydroxide (0.8 g, 20 mmol) in water 5 ml was added. The mixture was heated to reflux for another 2 hours. Most of ethanol was evaporated under reduce pressure. The aqueous was extracted with ether (30 ml × 3). The ether layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a product.

Example 127

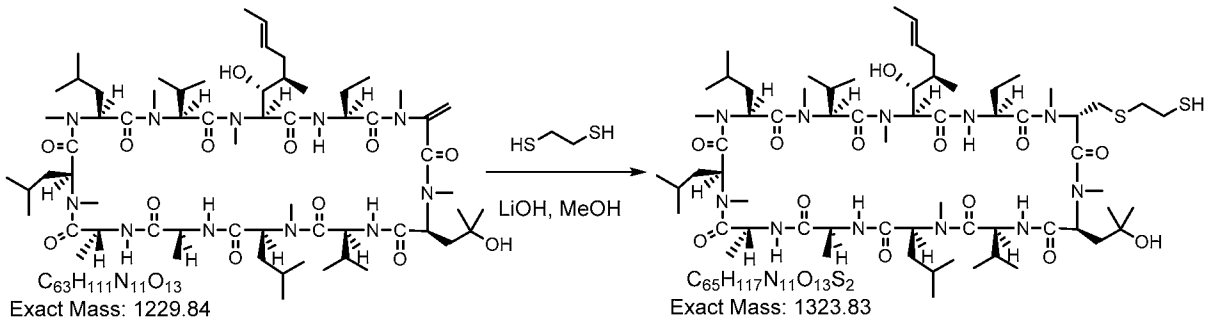
[(S)-((*E*-4-Diethylamino-2-propyl-2-butene)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.30 g, 0.24 mmol) and E-4-diethylamino-2-propyl-2-buten-1-thiol (0.48 g, 2.38 mmol) were dissolved in methanol (15 ml), followed by adding lithium hydroxide (60 mg, 2.50 mmol). The mixture was stirred at room temperature overnight. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a product [Molecular Formula: $C_{74}H_{134}N_{12}O_{13}S$; Exact Mass: 1430.99; MS (m/z): 1431.80 $(M+1)^+$; TLC R_f: 0.20 (ethyl acetate/methanol = 5/1); HPLC RT: 13.40 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 128

[(S)-(2-Mercaptoethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



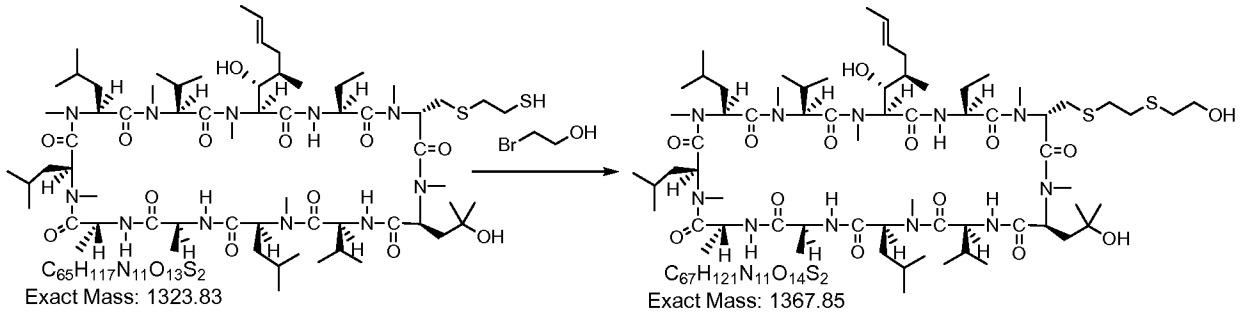
$C_{63}H_{111}N_{11}O_{13}$
Exact Mass: 1229.84
Molecular Weight: 1230.65

$C_{65}H_{117}N_{11}O_{13}S_2$
Exact Mass: 1323.83
Molecular Weight: 1324.84

[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.36 g, 0.29 mmol) and 1,2-ethanedithiol (0.26 g, 2.77 mmol) were dissolved in methanol (15 ml), followed by adding lithium hydroxide (65 mg, 2.71 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a pure product [Molecular Formula: $C_{65}H_{117}N_{11}O_{13}S_2$; Exact Mass: 1323.83; MS (m/z): 1324.39 $(M+1)^+$; TLC R_f: 0.28 (ethyl acetate/methanol = 5/1); HPLC RT: 15.19 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 129

[(S)-(2-(2-Hydroxyethylthio)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



$C_{65}H_{117}N_{11}O_{13}S_2$
Exact Mass: 1323.83
Molecular Weight: 1324.84

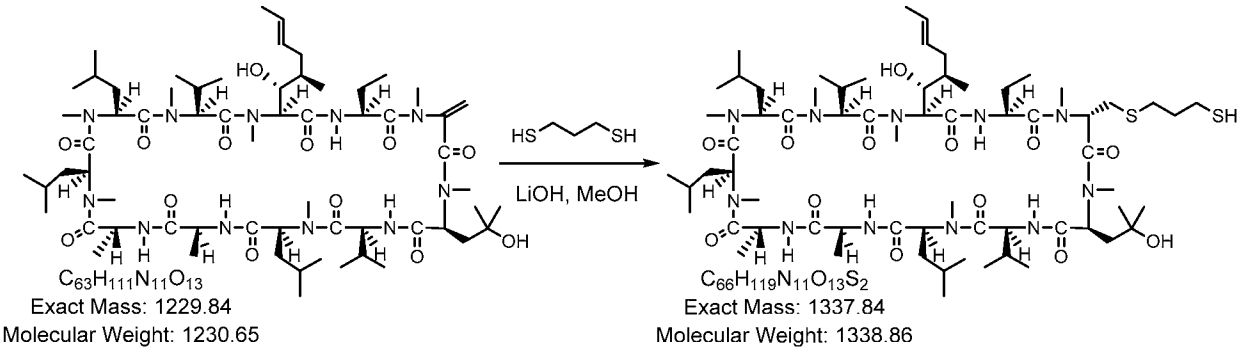
$C_{67}H_{121}N_{11}O_{14}S_2$
Exact Mass: 1367.85
Molecular Weight: 1368.89

To a mixture of [(S)-(2-mercaptoethyllthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (90 mg, 0.07 mmol) and lithium hydroxide (45 mg, 1.87 mmol) in methanol (10 ml) was added 2-bromoethanol (0.20 g, 1.61 mmol). The mixture was stirred at room

temperature for 6 h. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a pure product [Molecular Formula: $C_{67}H_{121}N_{11}O_{14}S_2$; Exact Mass: 1367.85; MS (m/z): 1368.61 $(M+1)^+$; TLC R_f: 0.24 (ethyl acetate/methanol = 4/1); HPLC RT: 13.60 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 130

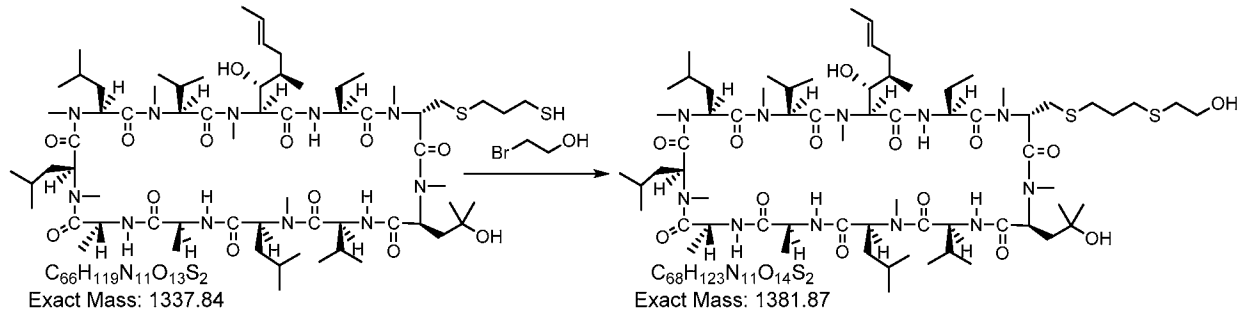
[(S)-(3-Mercaptopropylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.30 g, 0.24 mmol) and 1,3-propanedithiol (0.26 g, 2.41 mmol) were dissolved in methanol (15 ml), followed by adding lithium hydroxide (59 mg, 2.44 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a pure product [Molecular Formula: $C_{66}H_{119}N_{11}O_{13}S_2$; Exact Mass: 1337.84; MS (m/z): 1338.38 $(M+1)^+$; TLC R_f: 0.25 (ethyl acetate/methanol = 5/1); HPLC RT: 15.70 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 131

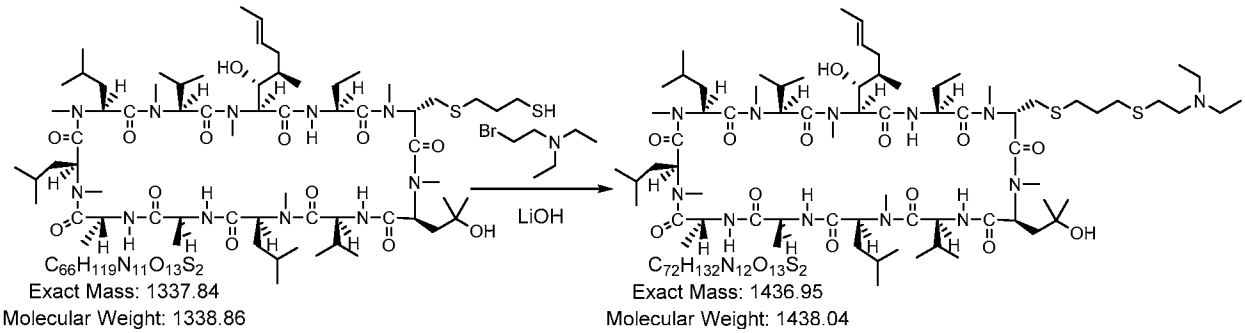
[(S)-(3-(2-Hydroxyethylthio)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



To a mixture of [(S)-(3-mercaptopropyllthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (100 mg, 0.07 mmol) and lithium hydroxide (45 mg, 1.87 mmol) in methanol (10 ml) was added 2-bromoethanol (0.20 g, 1.61 mmol). The mixture was stirred at room temperature for 6 h. After removal of solvent, the residue was dissolved in dichloromethane (50 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a pure product [Molecular Formula: $C_{68}H_{123}N_{11}O_{14}S_2$; Exact Mass: 1381.87; MS (m/z): 1382.45 $(M+1)^+$; TLC R_f: 0.25 (ethyl acetate/methanol = 5/1); HPLC RT: 13.85 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 132

[(S)-(3-(2-Diethylaminoethylthio)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

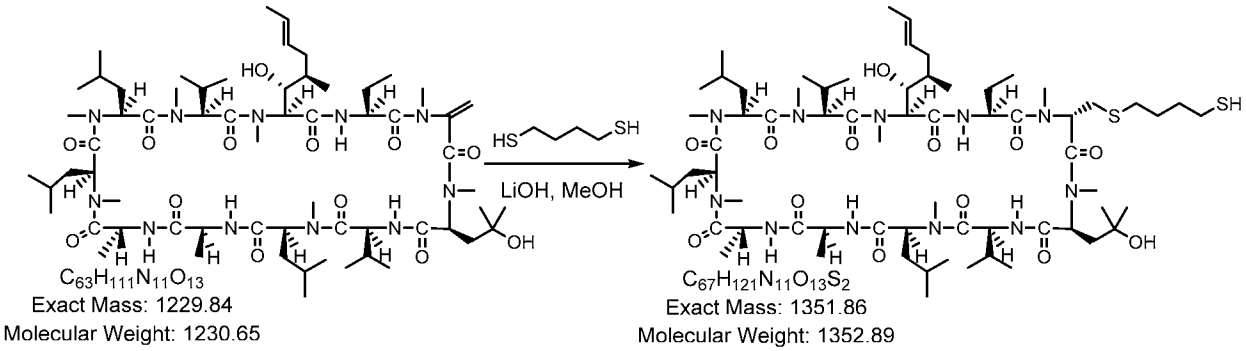


To a mixture of [(S)-(3-mercaptopropyllthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (200 mg, 0.15 mmol) and lithium hydroxide (53 mg, 2.21 mmol) in methanol (20 ml) was added 2-bromo-N,N-diethylethylamine hydrobromide (0.60 g, 2.31 mmol). The mixture was stirred at room temperature for 7 hours. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was

purified by flash chromatography using dichloromethane/methanol as eluent to give a product [Molecular Formula: $C_{72}H_{132}N_{12}O_{13}S_2$; Exact Mass: 1436.95; MS (m/z): 1437.49 $(M+1)^+$; TLC R_f: 0.20 (ethyl acetate/methanol = 4/1); HPLC RT: 11.96 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 133

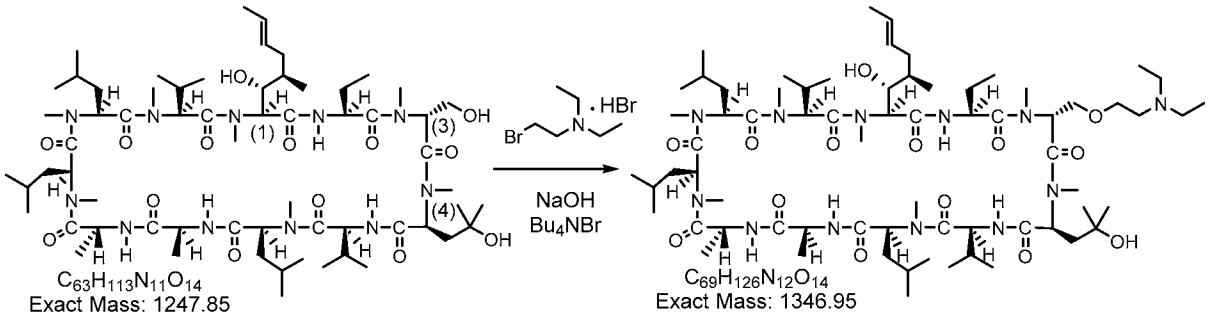
[(S)-(4-Mercaptobutylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) and 1,4-butanedithiol (0.30 g, 2.27 mmol) were dissolved in methanol (15 ml), followed by adding lithium hydroxide (50 mg, 2.08 mmol). The mixture was stirred at room temperature overnight. After removal of solvent, the residue was dissolved in dichloromethane (30 ml). The dichloromethane solution was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography using dichloromethane/methanol as eluent to give a product [Molecular Formula: $C_{67}H_{121}N_{11}O_{13}S_2$; Exact Mass: 1351.88; MS (m/z): 1352.39 $(M+1)^+$; TLC R_f: 0.27 (ethyl acetate/methanol = 6/1); HPLC RT: 16.12 min. (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 134

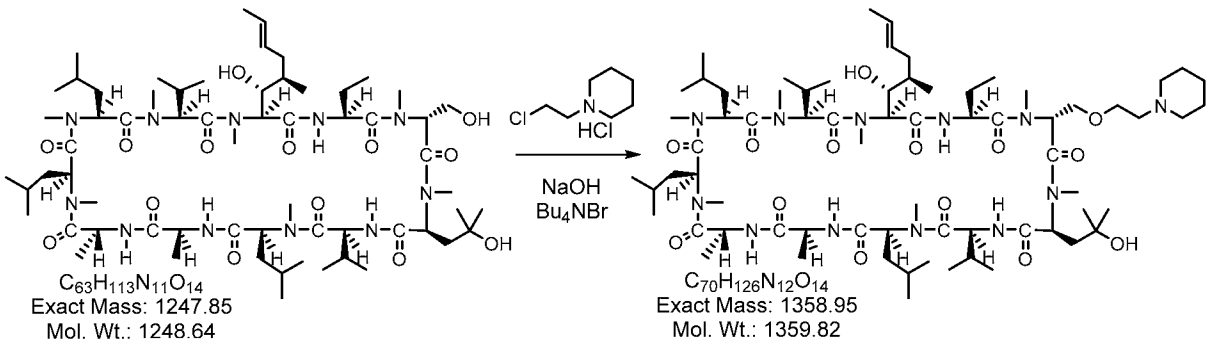
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0276] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) in benzene (30 ml) were added a solution of sodium hydroxide (1.00 g, 25 mmol) in water (2 ml), 2-bromo-N,N-diethylethylamine hydrobromide (MW: 261, 2.80 g, 10.72 mmol) and tetra-n-butylammonium bromide (0.2 g, 0.62 mmol). The mixture was stirred at 30 °C for 20 hours. Then ice water (30 ml) was added and the mixture was separated. The aqueous layer was extracted with dichloromethane (25 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 240 mg of product [Molecular Formula: $C_{69}H_{126}N_{12}O_{14}$; Exact Mass: 1346.95; MS (m/z): 1347.59 $(M+1)^+$; TLC Rf: 0.41 (dichloromethane/methanol = 9/1); HPLC RT: 12.20 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 135

[(R)-(2-(N-Piperidinyl)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

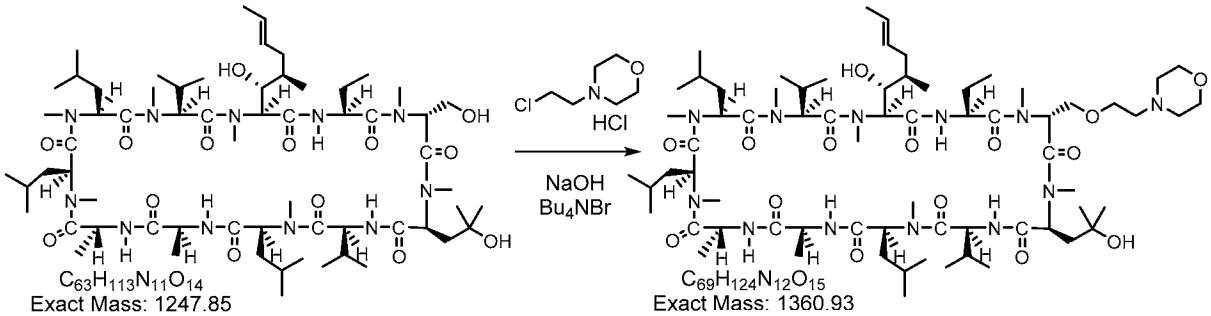


[0277] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (300 mg, 0.24 mmol) in benzene (15 ml) were added sodium hydroxide (0.38 g. 9.60 mmol), tetramethylammonium hydroxide pentahydrate (0.44 g, 2.40 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (MW: 184.10, 0.44 g, 2.40 mmol). The mixture was stirred at 30 °C for 36 hours. Then ice water (20 ml) was added and the mixture was

separated. The aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with dichloromethane/methanol (95/5) as eluent to give 100 mg of pure product [Molecular Formula: $C_{70}H_{126}N_{12}O_{14}$; Exact Mass: 1358.95; MS (m/z): 1359.69 $(M+1)^+$, 1381.75 $(M+Na)^+$; TLC R_f: 0.05 (dichloromethane/methanol = 20/1); HPLC RT: 12.43 min (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 136

[(R)-(2-(N-Morpholino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



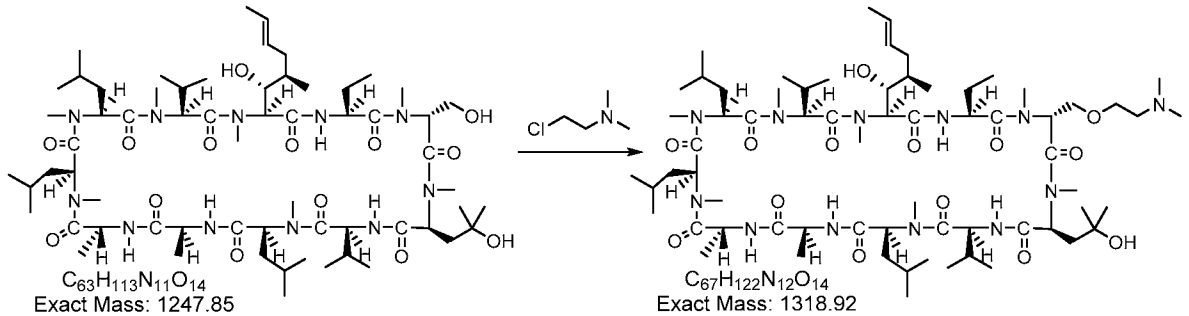
$C_{63}H_{113}N_{11}O_{14}$
Exact Mass: 1247.85
Mol. Wt.: 1248.64

$C_{69}H_{124}N_{12}O_{15}$
Exact Mass: 1360.93
Mol. Wt.: 1361.79

[0278] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.50 g, 0.40 mmol) in benzene (20 ml) were added sodium hydroxide (0.64 g, 16.00 mmol), tetramethylammonium hydroxide pentahydrate (0.72 g, 4.00 mmol) and 4-(2-chloroethyl)morphorline hydrochloride (MW: 186.08, 0.74 g, 4.00 mmol). The mixture was stirred at 30 °C for a week. Then ice water (20 ml) was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with dichloromethane/methanol (95/5) as eluent to give 60 mg of product [Molecular Formula: $C_{69}H_{124}N_{12}O_{15}$; Exact Mass: 1360.93; MS (m/z): 1361.63 $(M+1)^+$, 1383.75 $(M+Na)^+$; TLC R_f: 0.10 (dichloromethane/methanol = 5:1); HPLC RT: 11.49 min (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 137

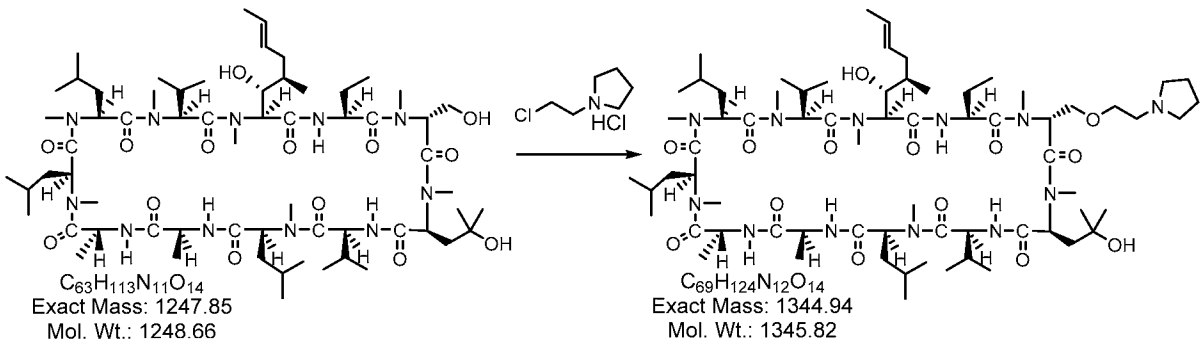
[(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0279] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.37 g, 0.30 mmol) in benzene (15 ml) were added sodium hydroxide (0.48 g. 12.00 mmol), tetramethylammonium hydroxide pentahydrate (0.54 g, 3.00 mmol) and 3-dimethylaminoethyl chloride hydrochloride (0.43 g, 3.00 mmol). The mixture was stirred at 30 °C for 36 hours. Then ice water (20 ml) was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with dichloromethane/methanol (95/5) as eluent to give 90 mg of pure product [Molecular Formula: $C_{67}H_{122}N_{12}O_{14}$; Exact Mass: 1318.92; MS (m/z):1319.70 $(M+1)^+$, 1341.80 $(M+Na)^+$); TLC R_f: 0.05 (dichloromethane/methanol = 5:1); HPLC RT: 11.43 min (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 138

[(R)-(2-(N-Pyrrolidinyl)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

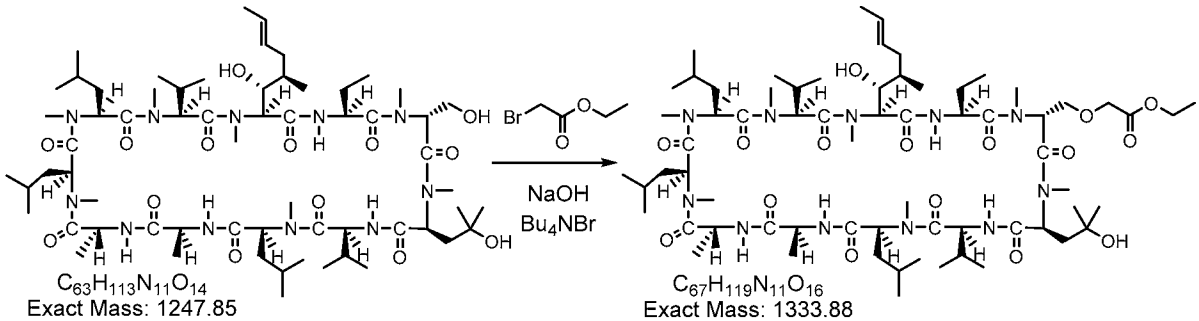


[0280] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.38 g, 0.30 mmol) in benzene (15 ml) were added sodium hydroxide (0.48 g, 12.00 mmol), tetramethylammonium hydroxide pentahydrate (0.54 g, 3.00 mmol) and 1-(2-chloroethyl)pyrrolidine hydrochloride (0.44 g, 3.00 mmol). The mixture was stirred at 30

°C for 36 hours. Then ice water (20 ml) was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with dichloromethane/methanol (95/5) as eluent to give to give 120 mg of the expected isomer [Molecular Formula: $C_{69}H_{124}N_{12}O_{14}$; Exact Mass: 1344.94; MS (m/z): 1345.62 $(M+1)^+$, 1367.76 $(M+Na)^+$; TLC R_f: 0.05 (dichloromethane/methanol = 10/1); HPLC RT: 12.09 min (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 139

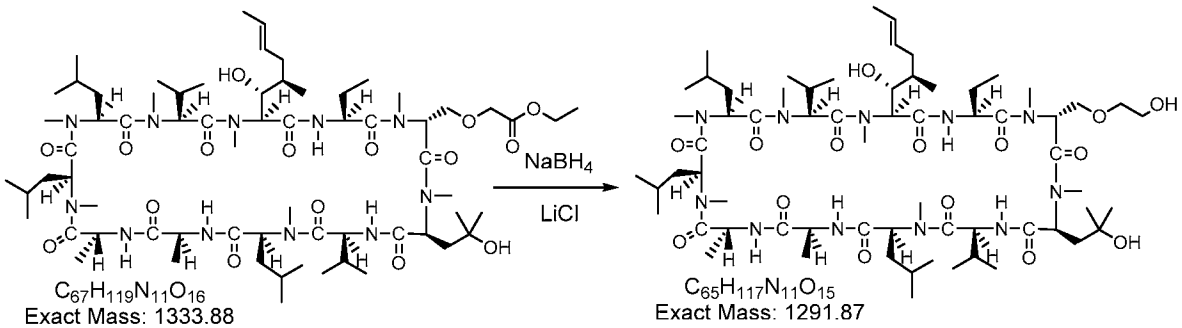
[(R)-(Ethoxycarbonylmethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0281] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.36 g, 0.29 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (0.60 g, 15.00 mmol) in water (1 ml), ethyl bromoacetate (1.60 g, 9.58 mmol) and tetra-n-butylammonium bromide (0.20 g, 0.62 mmol). The mixture was stirred at room temperature for 10 hours. After diluted with ice water, the mixture was separated. The aqueous layer was extracted with dichloromethane (15 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give the product [Molecular formula: $C_{67}H_{119}N_{11}O_{16}$; Exact Mass: 1333.88; MS (m/z): 1334.50 $(M+1)^+$; TLC R_f: 0.35 (dichloromethane/methanol = 95/5); HPLC RT: 15.16 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% NH_4OAc in water; operation temperature: 64 °C; Detector: 210 nm)].

Example 140

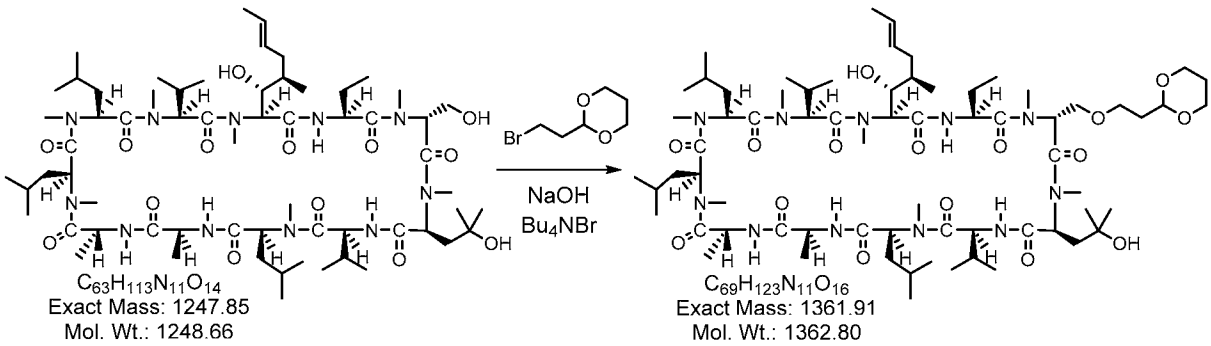
[(R)-(2-Hydroxyethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0282] To a solution of [(R)-(ethoxycarbonylmethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.23 g, 0.17 mmol) in methanol (30 ml) were added lithium chloride (0.30 g, 7.14 mmol) and sodium borohydride (0.66 g, 17.46 mmol) in portions. After addition, the mixture was stirred at room temperature overnight. Most solvent was then evaporated under reduced pressure. Ethyl acetate (50 ml) and water (50 ml) were added. The ethyl acetate layer was separated and washed with brine (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified on silica gel column with (dichloromethane/methanol = 95/5) to give the product [Molecular formula: $C_{65}H_{117}N_{11}O_{15}$; Exact Mass: 1291.87; MS (m/z): 1292.51$(M+1)^+$; TLC Rf: 0.28 (dichloromethane/methanol = 9/1); HPLC RT: 12.55 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 141

[(R)-(2-(1,3-Dioxan-2-yl)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

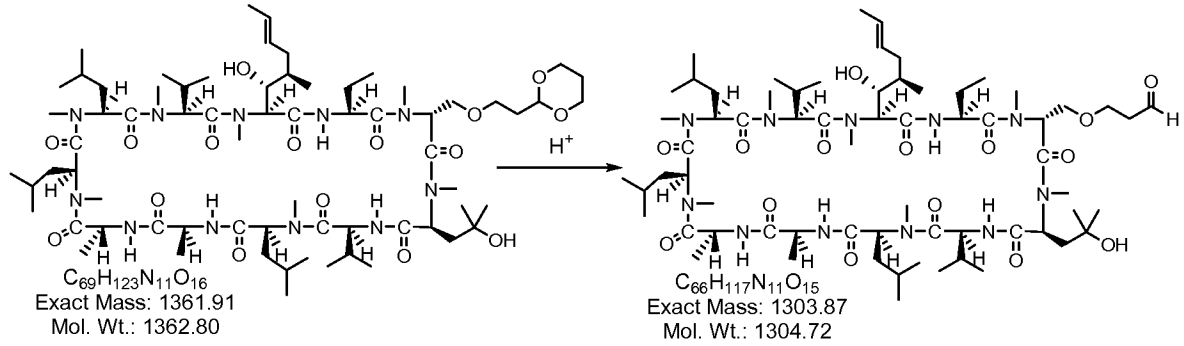


[0283] [(R)-Hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (5.00 g, 4.01 mmol) was dissolved in benzene (100 ml). 2-(2-Bromoethyl)-1,3-dioxane (7.82g, 40.10 mmol), tetra-n-butylammonium bromide (0.99 g, 3.09 mmol), sodium hydroxide (3.21 g, 8.02 mmol) and water (3.3 ml) were added. The reaction mixture was stirred at 35 °C for nine hours. And the stirring was continued overnight at room temperature. Then 50

ml of brine was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel with hexane/acetone as eluent, 1.50 g of product obtained [Molecular Formula: $C_{69}H_{123}N_{11}O_{16}$; Exact Mass: 1361.91; (m/z): 1362.64 $(M+1)^+$, 1384.85 $(M+Na)^+$].

Example 142

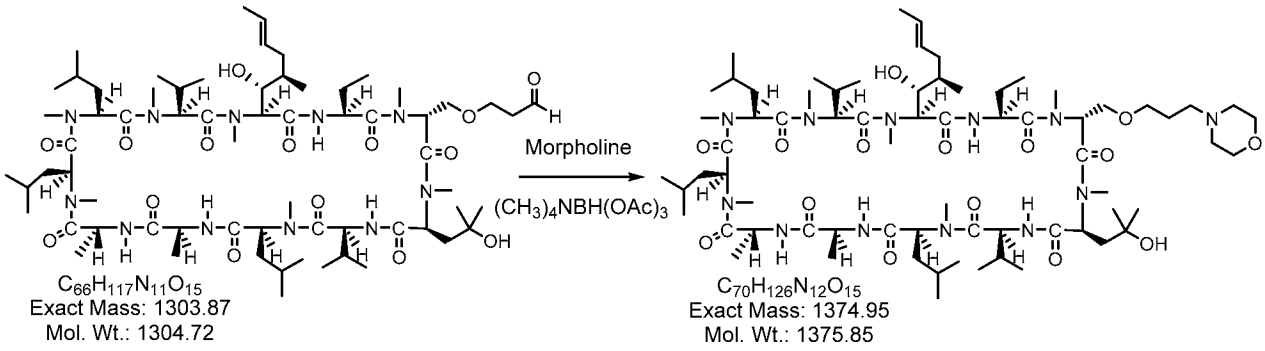
[(R)-(2-Formylethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0284] [(R)-(2-(1,3-Dioxan-2-yl)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (1.29 g, 0.95 mmol) was dissolved in dioxane (25 ml), followed by adding hydrochloric acid solution (1 N, 25 ml). The reaction mixture was stirred overnight at room temperature. Most of dioxane was evaporated under reduced pressure. Then the aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined ethyl acetate layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified on silica gel with hexane/acetone as eluent to give 600 mg of product [Molecular Formula: $C_{66}H_{117}N_{11}O_{15}$; Exact Mass: 1303.87; MS (m/z): 1304.59 $(M+1)^+$, 1326.78 $(M+Na)^+$; HPLC RT: 14.2 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 143

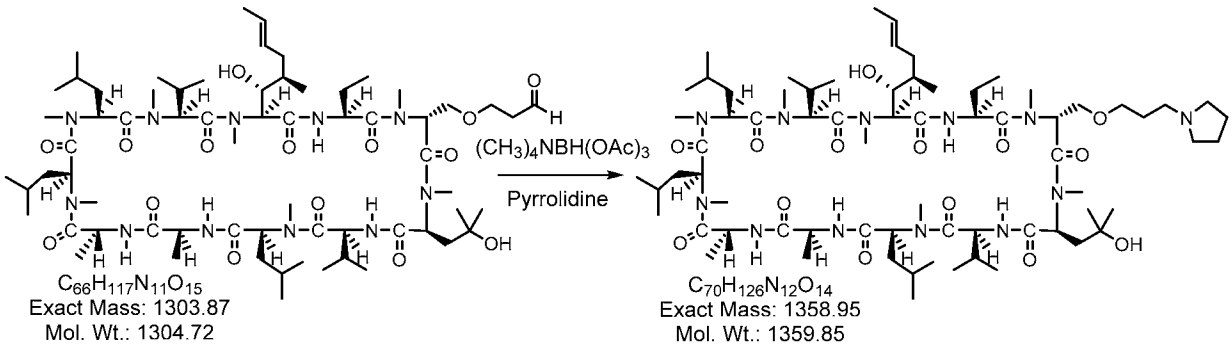
[(R)-(3-(N-Morpholino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0285] [(R)-(2-Formylethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (300 mg, 0.23 mmol) was dissolved in dichloromethane (15 ml). Morpholine (100 mg, 1.15 mmol) and tetramethylammonium triacetoxyborohydride (302 mg, 1.15 mmol) were added. The reaction mixture was stirred overnight at room temperature. Then sodium bicarbonate saturated solution (30 ml) and dichloromethane (15ml) were added and the mixture was separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 105 mg of pure product was obtained [Molecular Formula: $C_{70}H_{126}N_{12}O_{15}$; Exact Mass: 1374.95; MS (m/z): 1375.70 $(M+1)^+$, 1397.80 $(M+Na)^+$; TLC R_f: 0.37 (dichloromethane/methanol = 9/1); HPLC RT: 12.2 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 144

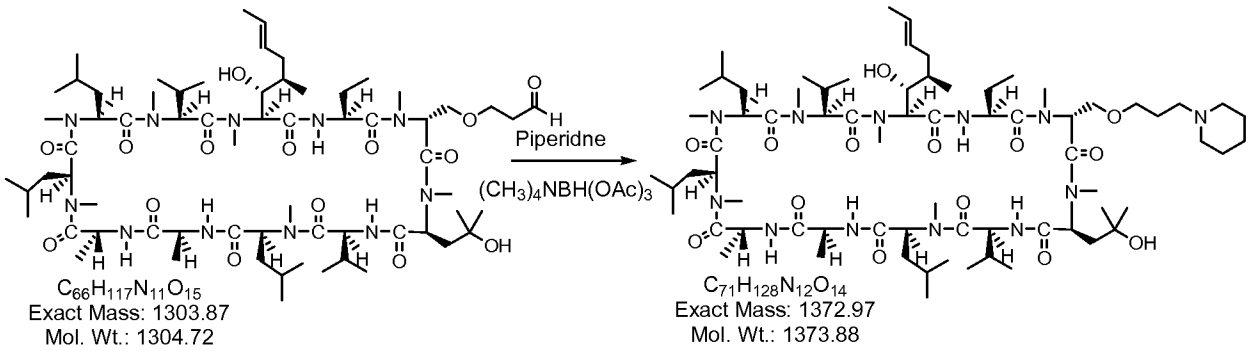
[(R)-(3-(N-Pyrrolidinyl)propoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0286] [(R)-(2-Formylethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (200 mg, 0.15 mmol) was dissolved in dichloromethane (15 ml). Pyrrolidine (95 mg, 1.34 mmol) and tetramethylammonium triacetoxyborohydride (353 mg, 1.34 mmol) were added. The reaction mixture was stirred overnight at room temperature. Then sodium bicarbonate saturated solution (30 ml) and dichloromethane (15 ml) were added and the mixture was separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 50 mg of pure product was obtained [Molecular Formula: $C_{70}H_{126}N_{12}O_{14}$; Exact Mass: 1358.95; MS (m/z): 1359.74 $(M+1)^+$, 1381.79 $(M+Na)^+$; TLC R_f: 0.40 (dichloromethane/methanol = 9/1); HPLC RT: 12.7 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 145

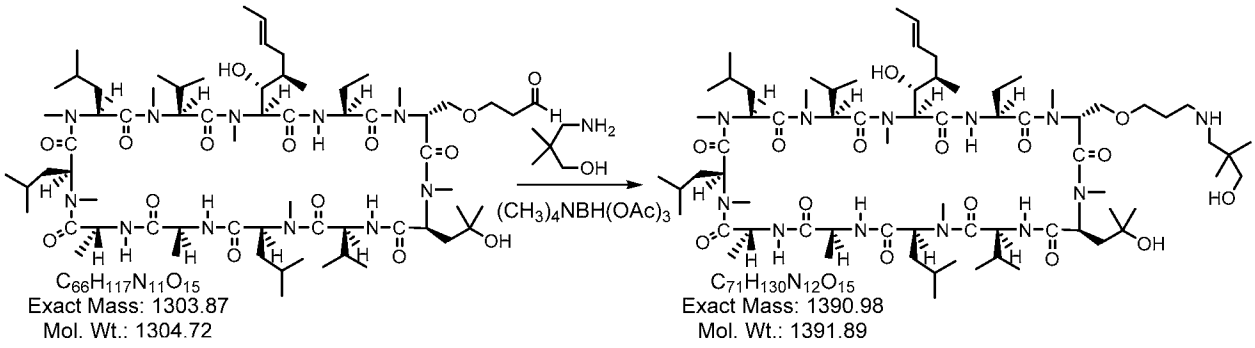
[(R)-(3-(N-Piperidinyl)propoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0287] [(R)-(2-Formylethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (200 mg, 0.15 mmol) was dissolved in dichloromethane (15 ml). Piperidine (114 mg, 1.34 mmol) and tetramethylammonium triacetoxyborohydride (353 mg, 1.34 mmol) were added. The reaction mixture was stirred overnight at room temperature. Then sodium bicarbonate saturated solution (30 ml) and dichloromethane (15 ml) were added and the mixture was separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 43 mg of product was obtained [Molecular Formula: $C_{71}H_{128}N_{12}O_{14}$; Exact Mass: 1372.97; (m/z): MS (m/z): 1373.79 $(M+1)^+$, 1395.86 $(M+Na)^+$; TLC R_f: 0.27 (dichloromethane/methanol = 9/1); HPLC RT: 17.8 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 146

[(R)-(3-(3-Hydroxy-2,2-dimetylpropylamino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

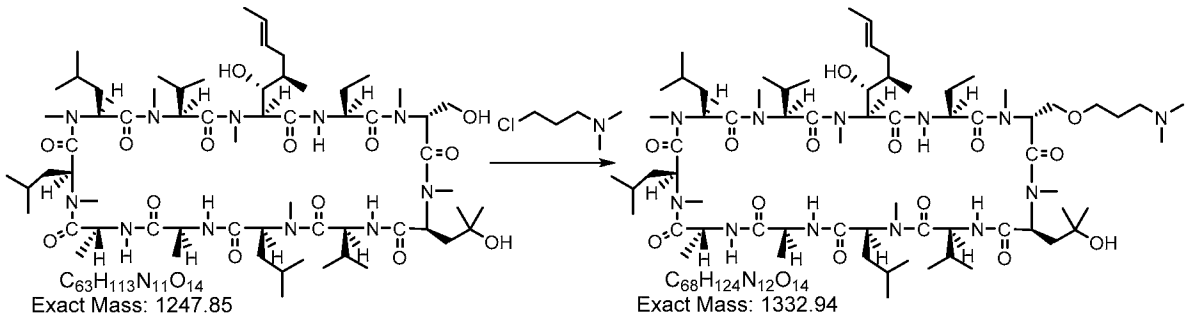


[0288] [(R)-(2-Formylethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (100 mg, 0.08 mmol) was dissolved in dichloromethane (15 ml). 3-Amino-2,2-dimethyl-1-propanol (40 mg, 0.39 mmol) and tetramethylammonium triacetoxyborohydride (100 mg, 0.39 mmol) were added. The reaction mixture was stirred at room temperature for 6 hours.

Then sodium bicarbonate saturated solution (30 ml) and dichloromethane (15 ml) were added and the mixture was separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 10 mg of pure product was obtained [Molecular Formula: $C_{71}H_{130}N_{12}O_{15}$; Exact Mass: 1390.98; MS (m/z): 1391.64 $(M+1)^+$, 1413.77 $(M+Na)^+$; TLC R_f: 0.37 (dichloromethane/methanol = 9/1); HPLC RT: 11.46 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 147

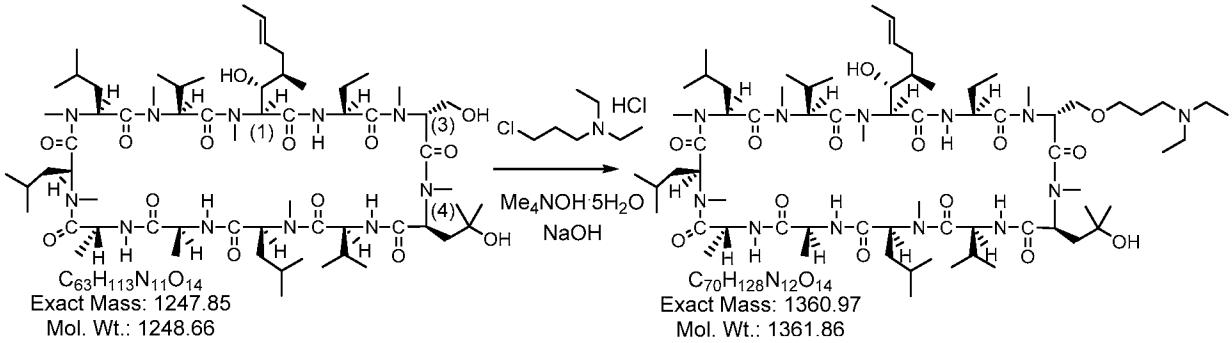
[(R)-(3-(N,N-Dimethylamino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0289] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.38 g, 0.30 mmol) in benzene (15 ml) were added sodium hydroxide (0.48 g, 12.00 mmol), tetramethylammonia hydroxide (0.54 g, 3.0 mmol) and 3-dimethylaminoethyl chloride hydrochloride (0.43 g, 3.00 mmol). The mixture was stirred at 30 °C for 36 hours. Then ice water (20 ml) was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with dichloromethane/methanol (95/5) as eluent to give to give 70 mg of pure product [Molecular Formula: $C_{68}H_{124}N_{12}O_{14}$; Exact Mass: 1332.94. MS (m/z): 1333.64 $(M+1)^+$, 1355.73 $(M+Na)^+$; TLC R_f: 0.04 (dichloromethane/methanol = 5/1); HPLC RT: 11.78 min (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 148

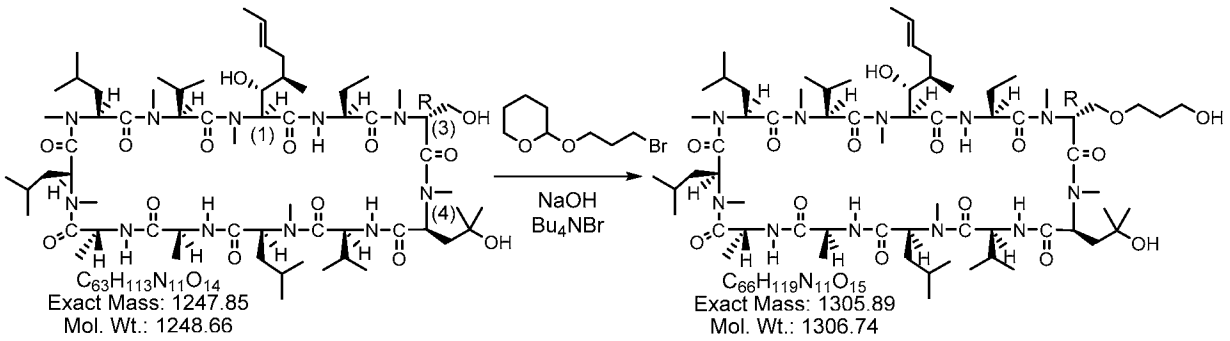
[(R)-(3-(N,N-Diethylamino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0290] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.20 mmol) in benzene (15 ml) were added a solution of sodium hydroxide (400 mg, 10.00 mmol) in water (0.5 ml), 3-diethylaminepropyl chloride hydrochloride (500 mg, 2.69 mmol) and tetramethylammonium hydroxide pentahydrate (430 mg, 2.41 mmol). The mixture was stirred at 32 °C for 4 days. Then ice water (30 ml) was added and the mixture was separated. The aqueous layer was extracted with dichloromethane (50 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 95/5) to give 120 mg of product [Molecular Formula: $C_{70}H_{128}N_{12}O_{14}$; Exact Mass: 1360.97; MS (m/z): 1361.72 $(M+1)^+$; TLC Rf: 0.38 (dichloromethane/methanol = 9/1); HPLC RT: 16.71 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 149

[(R)-(3-Hydroxypropoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

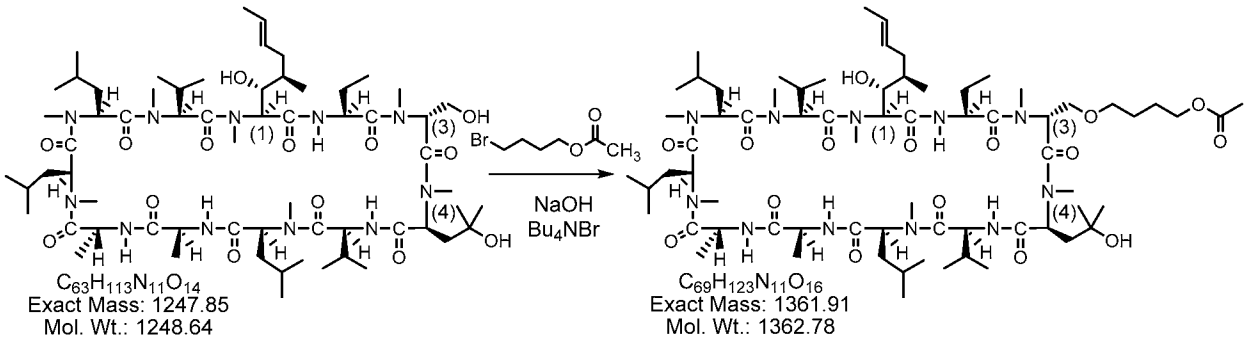


[0291] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) in benzene (30 ml) were added a solution of sodium

hydroxide (1.00 g, 25 mmol) in water (2 ml), 2-(3-bromopropoxy)tetrahydro-2H-pyran (2.50 g, 11.21 mmol) and tetra-n-butylammonium bromide (0.2 g, 0.62 mmol). The mixture was stirred at 30 °C for 4 hours. Then ice water (30 ml) was added and the mixture was separated. The aqueous layer was extracted with dichloromethane (25 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give the product [Molecular Formula: $C_{66}H_{119}N_{11}O_{15}$; Exact Mass: 1305.89; MS (m/z): 1306.46 $(M+1)^+$; TLC Rf: 0.38 (dichloromethane/methanol = 9/1); HPLC RT: 12.94 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 150

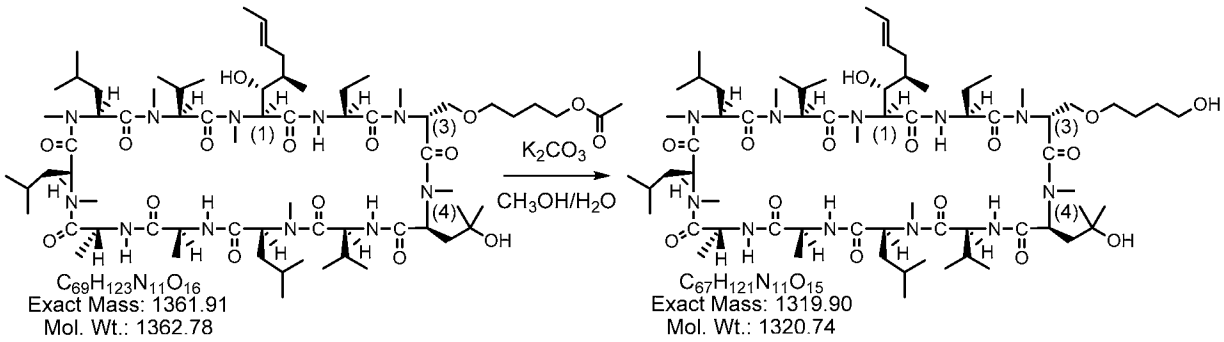
[(R)-(4-Acetoxybutyloxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0292] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (0.34 g, 0.27 mmol) in benzene (10.0 ml) were added 4-bromobutyl acetate (1.56 ml, d 1.348, 10.81 mmol), tetra-n-butylammonium bromide (0.30 g, 0.94 mmol) and sodium hydroxide (0.70 g, 17.6 mmol). The mixture was stirred at room temperature for two hours and then washed with brine, dried over magnesium sulfate. After removal of solvent under reduced pressure, the residue was purified by chromatography on silica gel to give pure product [Molecular formula: $C_{69}H_{123}N_{11}O_{16}$; Exact Mass: 1361.91; MS (m/z): 1362.51$(M+1)^+$, 1385.77 $(M+Na)^+$].

Example 151

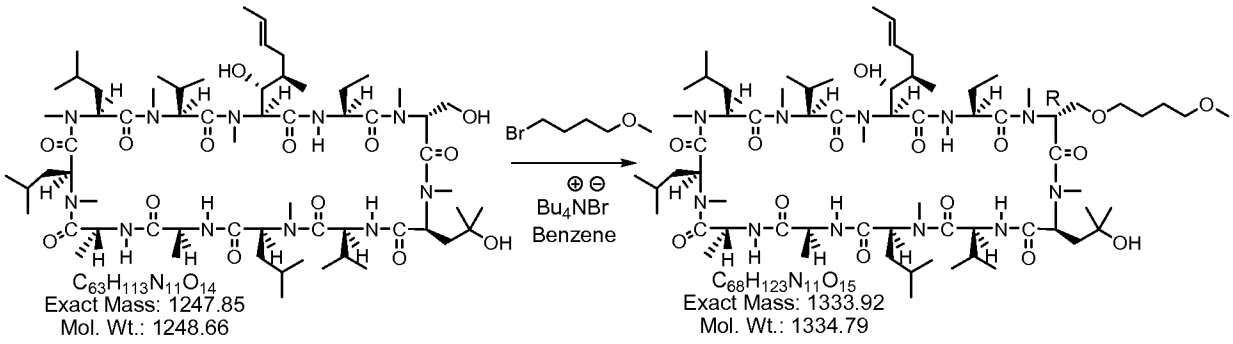
[(R)-(4-Hydroxylbutoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0293] [(R)-(4-Acetoxybutyloxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (49 mg, 0.036 mmol) was dissolved in methanol (5 ml). Water (3 ml) and potassium carbonate (99 mg, 0.72 mmol) were added and the mixture was stirred for two hours. After removal of methanol, the residue was dissolved in ethyl acetate (6 ml). The ethyl acetate layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with ethyl acetate/methanol as eluent to give 22 mg of the pure product [Molecular formula: $C_{67}H_{121}N_{11}O_{15}$; Exact Mass: 1319.90; MS (m/z): 1320.58 $(M+1)^+$, 1342.78 $(M+Na)^+$; TLC R_f: 0.20 (methylene/methanol = 25/1); HPLC RT: 13.62 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 152

[(R)-(4-Methoxylbutoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

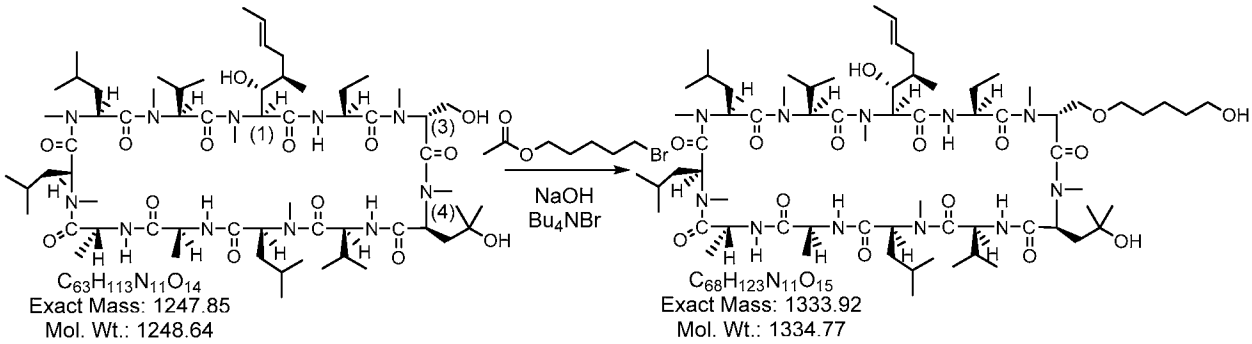


[0294] To a solution of [(S)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.624 g, 0.50 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (1.40 g, 35 mmol) in water (2 ml), 1-bromo-4-methoxybutane (0.84 g, 5.0 mmol) and tetra-n-butylammonium bromide (0.563 g, 1.75 mmol). The mixture was stirred at room temperature overnight and then at 30 °C for 4 hours. Then ice water (30 ml) was added and separated. The aqueous layer was extracted with dichloromethane (25 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and

concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 20:1) to give 50 mg of product [Molecular formula: $C_{68}H_{123}N_{11}O_{15}$; Exact Mass: 1333.92; MS (m/z): 1334.44 $(M+1)^+$, 1356.67 (M+Na); TLC Rf: 0.33 (dichloromethane/methanol = 20/1); HPLC RT: 15.52 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% NH_4OAc in water; operation temperature: 64 °C; Detector: 210 nm)].

Example 153

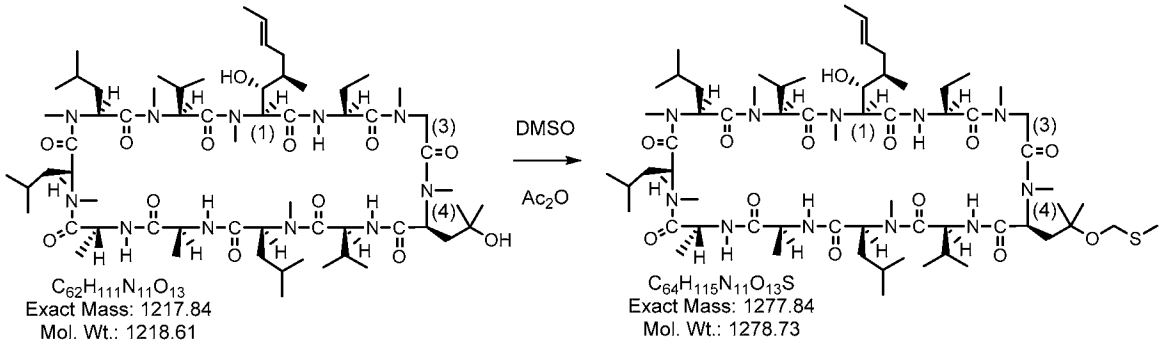
[(R)-(5-Hydroxypentyloxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0295] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) in benzene (30 ml) were added a solution of sodium hydroxide (1.00 g, 25 mmol) in water (2 ml), 5-bromopentyl acetate (2.20 g, 10.53 mmol) and tetra-n-butylammonium bromide (0.2 g, 0.62 mmol). The mixture was stirred at 30 °C for 10 hours. Then ice water (30 ml) was added and the mixture was separated. The aqueous layer was extracted with dichloromethane (25 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give the product [Molecular Formula: $C_{68}H_{123}N_{11}O_{15}$; Exact Mass: 1333.92; MS (m/z): 1334.46 $(M+1)^+$; TLC Rf: 0.30 (dichloromethane/methanol = 95/5); HPLC RT: 14.22 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 154

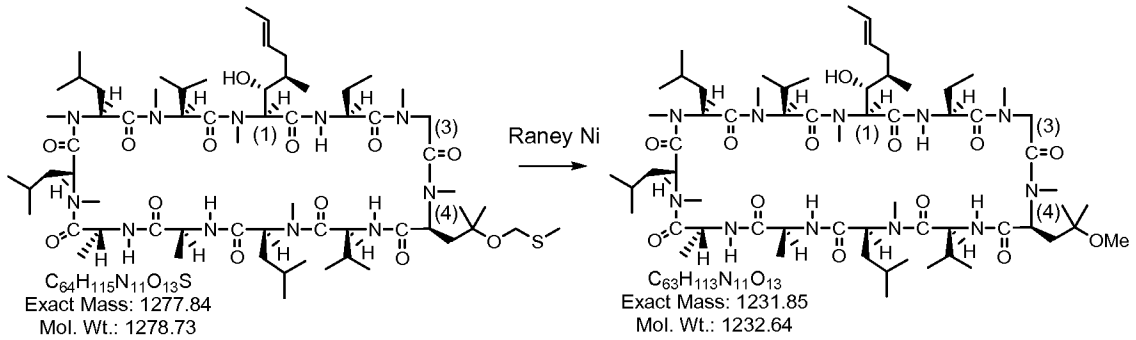
[(γ-(Methylthio)methoxy)-NMeLeu]-4-cyclosporin



[0296] To a solution of [(γ-hydroxy)-N-MeLeu]-4-cyclosporin (4.50 g, 3.70 mmol) in anhydrous dimethyl sulfoxide (25 ml) was added acetic anhydride (15 ml). The reaction mixture was stirred at room temperature for 17 hours. After diluted with ethyl acetate (75 ml), the mixture was washed with saturated sodium bicarbonate water solution and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified on silica gel chromatography with dichloromethane/methanol (98/2) as eluant to give 2.35 g of [(γ-methylthio)methoxy-N-MeLeu]-4-cyclosporin [Molecular Formula: $C_{64}H_{115}N_{11}O_{13}S$; Exact Mass: 1277.84; MS (m/z): 1300.70 $(M+Na)^+$; TLC R_f: 0.30 (dichloromethane/methanol = 95/5); HPLC RT: 19.57 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 155

[γ-(Methoxy)-NMeLeu]-4-cyclosporin

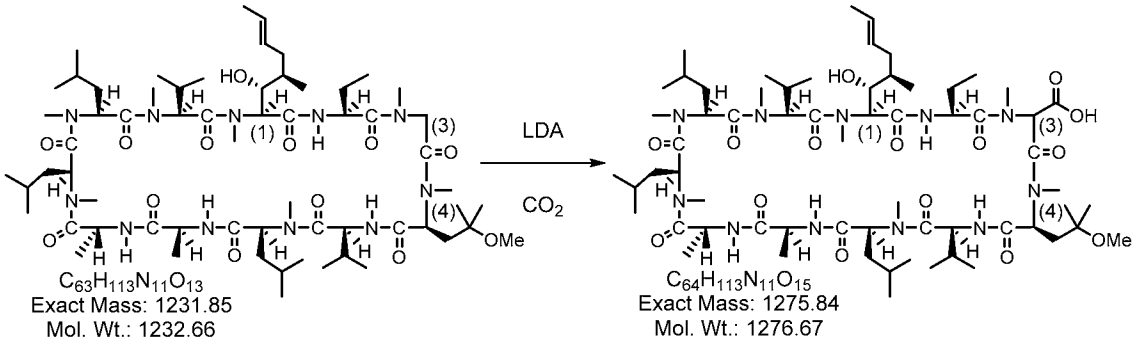


[0297] To a solution of [γ-(Methylthio)methoxy-N-MeLeu]-4-cyclosporin (1.20 g, 0.94 mmol) in anhydrous tetrahydrofuran (40 ml) was added Raney Ni (~ 2 g). The resulting suspension was stirred and heated to 60 °C for 30 minutes and the reaction was monitored by LC-MS. The reaction mixture was filtered and the filter cake was washed with

tetrahydrofuran. The filtrate was collected and evaporated under reduced pressure. The residue was purified by chromatography using eluant of ethyl acetate/methanol (97.5/2.5) to give 0.60 g of product [Molecular Formula: $C_{63}H_{113}N_{11}O_{13}$; Exact Mass: 1231.85; MS (m/z): 1232.70 $(M+1)^+$; TLC R_f: 0.46 (dichloromethane/methanol = 95/5); HPLC RT: 20.63 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 156

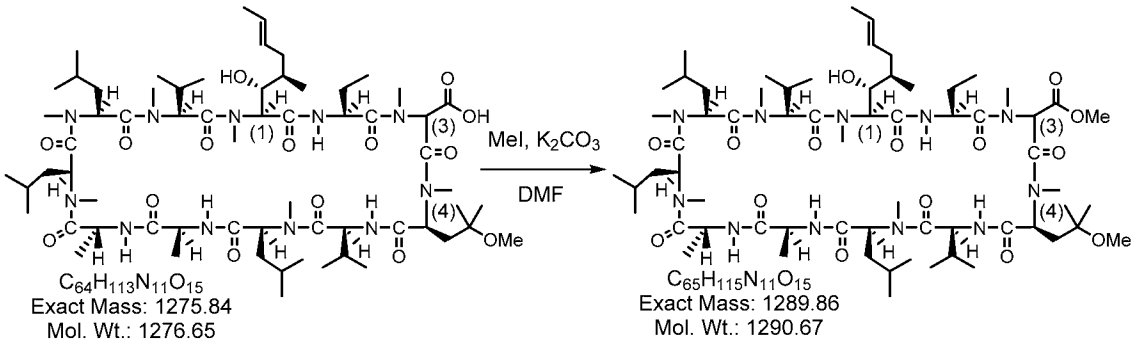
[α-Carboxy-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0298] n-Butyllithium (2.8 M in tetrahydrofuran/hexane, 5.00 ml, 14.00 mmol) was added to a solution of diisopropylamine (1.44 g, 14.30 mmol) in tetrahydrofuran (30 ml) at –78 °C under nitrogen atmosphere. After the mixture was stirred for one and half hour, a solution of [γ-(methoxy)-N-MeLeu]-4-cyclosporin (1.20 g, 0.97 mmol) in tetrahydrofuran (6 ml) was added slowly. The stirring was continued at –78 °C for 2 hours. Then carbon dioxide gas was bubbled into the reaction mixture for one hour. The mixture was allowed to warm to room temperature slowly and stirred for another 3 hours. After most of solvent was evaporated under reduced pressure, dichloromethane (30 ml) and water (30 ml) were added. The PH of the mixture was adjusted to around 5 by adding aqueous citric acid. The mixture was separated, and the dichloromethane layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give 1.20 g of crude product used for next step [Molecular Formula: $C_{64}H_{113}N_{11}O_{15}$; Exact Mass: 1275.84; MS (m/z): 1298.53$(M+Na)^+$].

Example 157

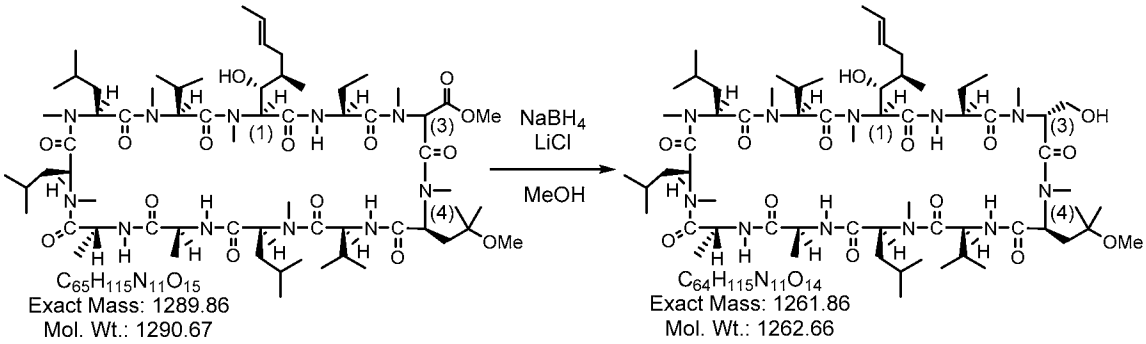
[α-Methoxycarbonyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0299] To a mixture of [α-carboxy]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (1.20 g. 0.94 mmol) and potassium carbonate (0.80 g, 5.79 mmol) in N,N-dimethylformamide (25 ml) was added iodomethane (0.80 g, 5.63 mmol). The mixture was stirred at room temperature overnight. Dichloromethane (75 ml) and water (30 ml) were added and the mixture was separated. The dichloromethane layer was washed with water (25 ml) and brine (25 ml), dried magnesium sulfate and concentrated under reduced pressure to give 1.10 g of crude product [Molecular Formula: $C_{65}H_{115}N_{11}O_{15}$; Exact Mass: 1289.86; MS (m/z): 1312.72$(M+Na)^+$].

Example 158

[(R)-α-Hydroxymethyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin

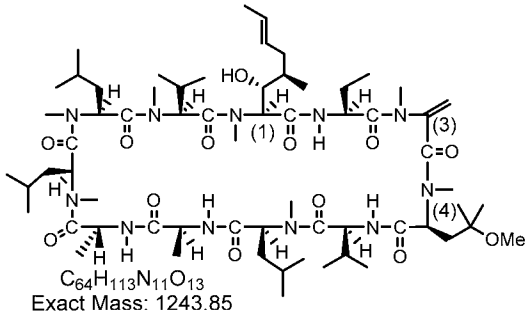


[0300] To a suspension of [α-methoxycarbonyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (1.10 g, 0.85 mmol) and lithium chloride (1.00 g, 23.53 mmol) in methanol (80 ml) was added sodium borohydride (2.00 g, 52.91 mmol) in portions. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. Dichloromethane (50 ml) and water (30 ml) were added and the mixture was separated. The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography

(dichloromethane/methanol = 97/3) to give 310 mg of product [Molecular Formula: $C_{64}H_{115}N_{11}O_{14}$; Exact Mass: 1261.86; MS (m/z): 1262.68 $(M+1)^+$].

Example 159

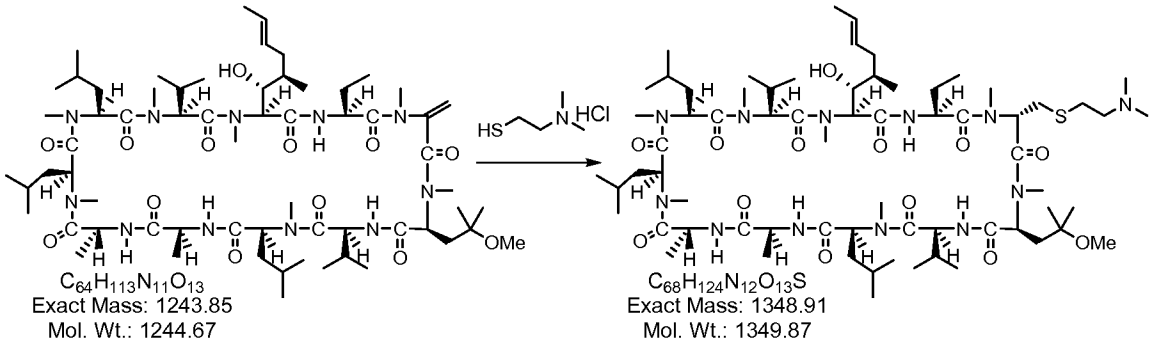
[α-Methylene-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0301] [α-Methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin was prepared according to the method described in Example 28 [Molecular Formula: $C_{64}H_{113}N_{11}O_{13}$; Exact Mass: 1243.85; MS (m/z): 1244.57 $(M+1)^+$; TLC R_f: 0.34 (hexane/acetone = 6/1); HPLC RT: 17.10 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifuloroacetic acid), operation temperature: 64 °C; detector: 210 nm].

Example 160

[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin

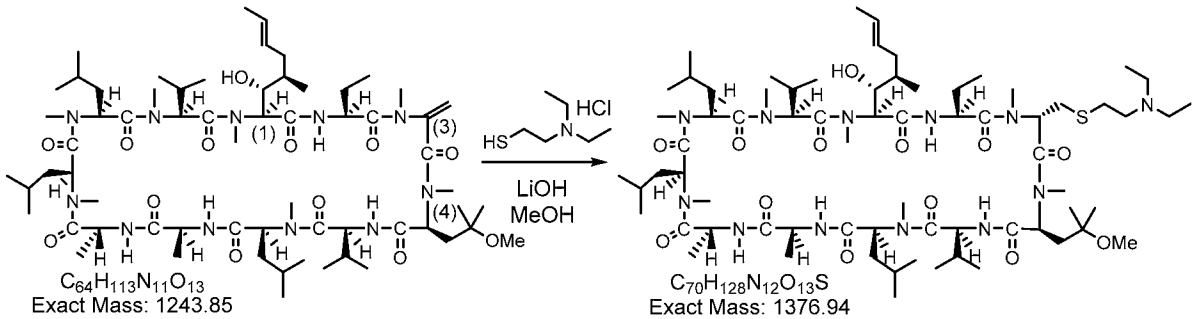


[0302] [α-Methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (0.24 g, 0.19 mmol) and 2-(N,N-dimethylamino)ethylthiol hydrochloride (0.27 g, 1.91 mmol) was dissolved in methanol (30 ml), followed by adding 20 equivalents of lithium hydroxide (46 mg, 1.90 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by flash chromatography using methylene chloride/methanol (96/4) as eluent to give 0.11 g of pure product [Molecular Formula: $C_{68}H_{124}N_{12}O_{13}S$; Exact Mass: 1348.93; MS (m/e): 1349.85 $(M+1)^+$, 1371.81 $(M+Na)^+$;

TLC R_f: 0.20 (ethyl acetate/methanol (5:1); HPLC RT: 12.42 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 161

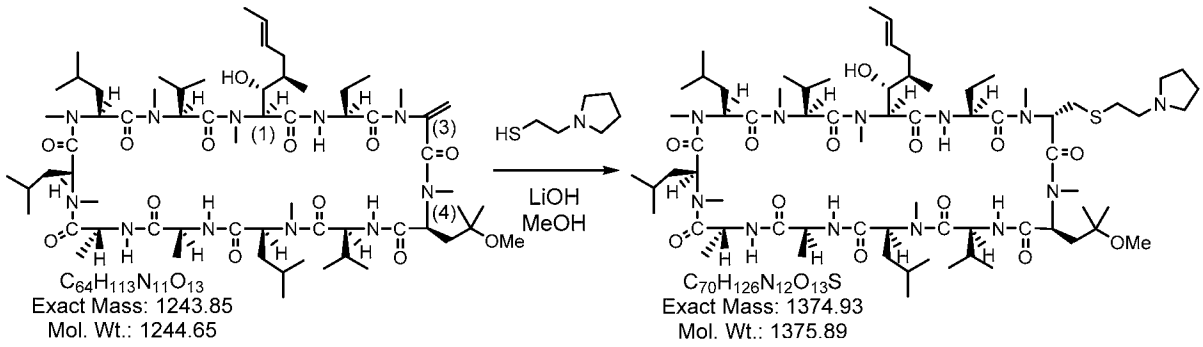
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0303] To a solution of [α-methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (280 mg, 0.23 mmol) and 2-diethylaminoethanethiol hydrochloride (570 mg, 3.37 mmol) in methanol (15 ml) was added lithium hydroxide (142 mg, 5.92 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Dichloromethane (80 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give 110 mg of product [Molecular Formula: $C_{70}H_{128}N_{12}O_{13}S$; Exact Mass: 1376.94; MS (m/z): 1377.67 $(M+1)^+$; TLC R_f: 0.35 (dichloromethane/methanol = 95/5); HPLC RT: 13.17 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 162

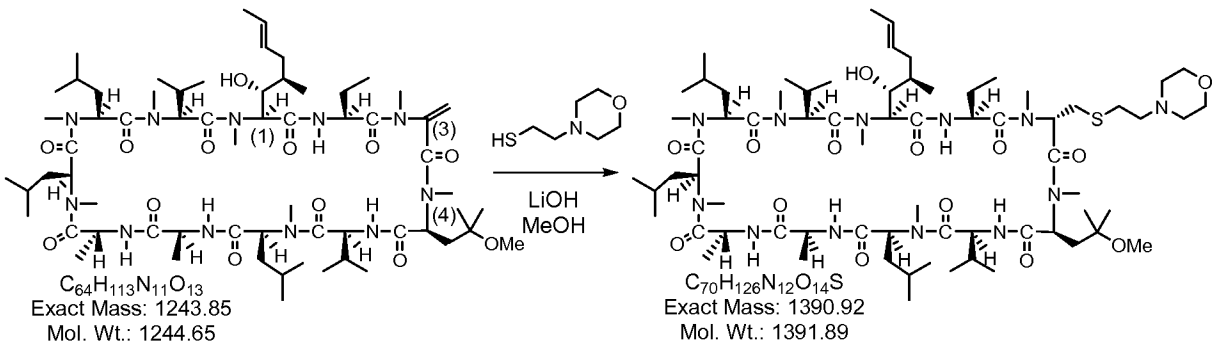
[(S)-(2-(N-Pyrrolidinyl)ethylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0304] To a solution of [α-methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (230 mg, 0.18 mmol) and 2-(N-pyrrolidinyl)ethanethiol (340 mg, 2.59 mmol) in methanol (15 ml) was added lithium hydroxide (120 mg, 5.00 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Dichloromethane (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 55 mg of product [Molecular Formula: $C_{70}H_{126}N_{12}O_{13}S$; Exact Mass: 1374.93; MS (m/z): 1375.57 $(M+1)^+$; TLC R_f: 0.29 (dichloromethane/methanol = 95/5); HPLC RT: 12.90 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 163

[(S)-(2-(N-Morpholino)ethylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin

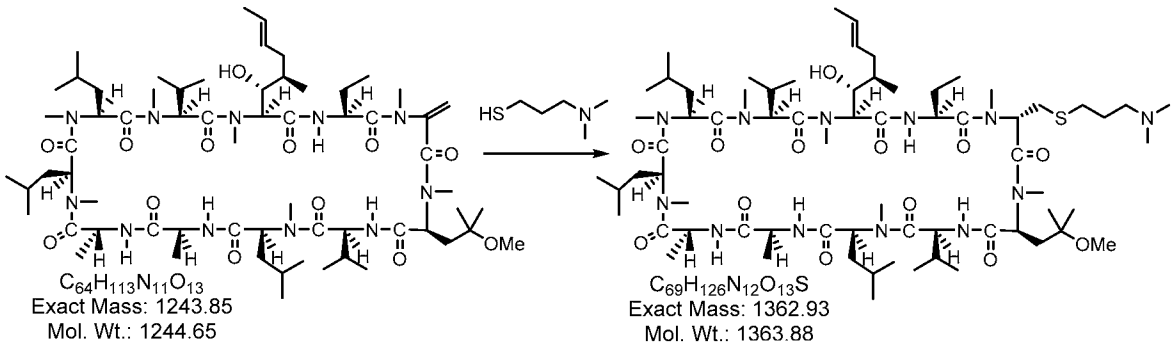


[0305] To a solution of [α-methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.20 mmol) and 2-morpholinoethanethiol (260 mg, 1.76 mmol) in methanol (15 ml) was added lithium hydroxide (120 mg, 5.00 mmol). The reaction mixture was stirred at room temperature overnight. Most of solvent was evaporated under reduced pressure.

Dichloromethane (60 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give 70 mg of product [Molecular Formula: $C_{70}H_{126}N_{12}O_{14}S$; Exact Mass: 1390.92; MS (m/z): 1391.58 $(M+1)^+$; TLC Rf: 0.38 (dichloromethane/methanol = 9/1); HPLC RT: 12.48 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 164

[(S)-(3-(N,N-Dimethylamino)propylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



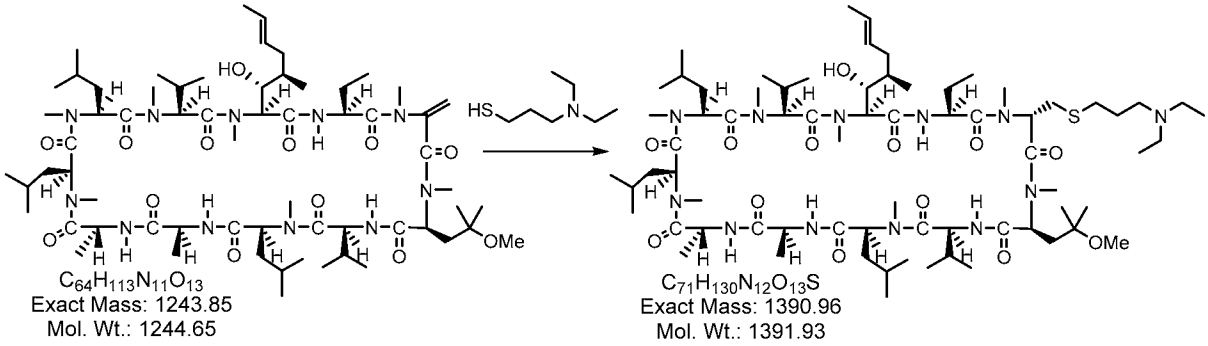
$C_{64}H_{113}N_{11}O_{13}$
Exact Mass: 1243.85
Mol. Wt.: 1244.65

$C_{69}H_{126}N_{12}O_{13}S$
Exact Mass: 1362.93
Mol. Wt.: 1363.88

[0306] [α-Methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) and 3-(N,N-dimethylamino)propylthiol (0.24 g, 2.00 mmol) were dissolved in methanol (20 ml), followed by adding 10 equivalents of lithium hydroxide (48 mg, 2.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by flash chromatography using methylene chloride/methanol as eluent to give 80 mg of pure product [Molecular Formula: $C_{69}H_{126}N_{12}O_{13}S$; Exact Mass: 1362.93; MS (m/e): 1363.70 $(M+1)^+$. TLC R_f: 0.20 (ethyl acetate/methanol = 10/1); HPLC RT: 12.82 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 165

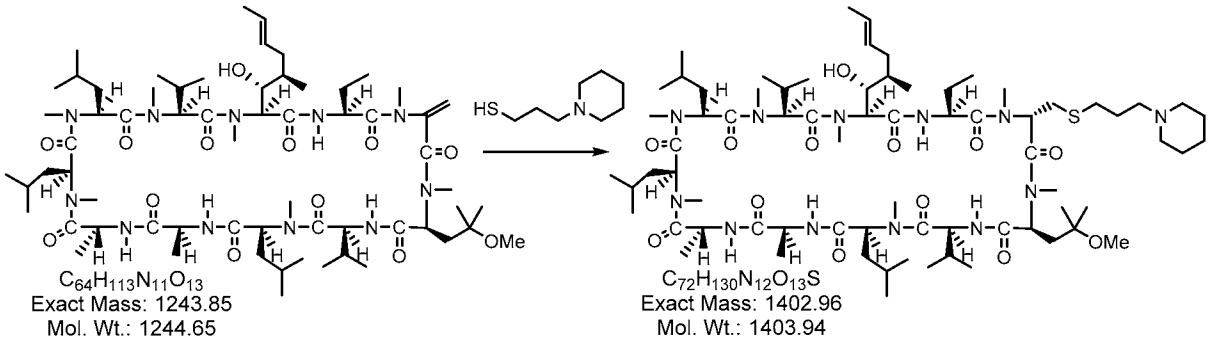
[(S)-(3-(N,N-Diethylamino)propylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0307] [α-Methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (0.25 g, 0.20 mmol) and 3-(N,N-diethylamino)propylthiol (0.30 g, 2.00 mmol) were dissolved in methanol (20 ml), followed by adding 10 equivalents of lithium hydroxide (48 mg, 2.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by flash chromatography using methylene chloride/methanol as eluent to give 120 mg of pure product [Molecular Formula: $C_{71}H_{130}N_{12}S$; Exact Mass: 1390.96; MS (m/e): 1391.64 $(M+1)^+$, 1413.79 $(M+Na)^+$; TLC R_f: 0.25 (ethyl acetate/methanol =10/1); HPLC RT: 13.57 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 166

[(S)-(3-(N-Piperidinyl)propylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin

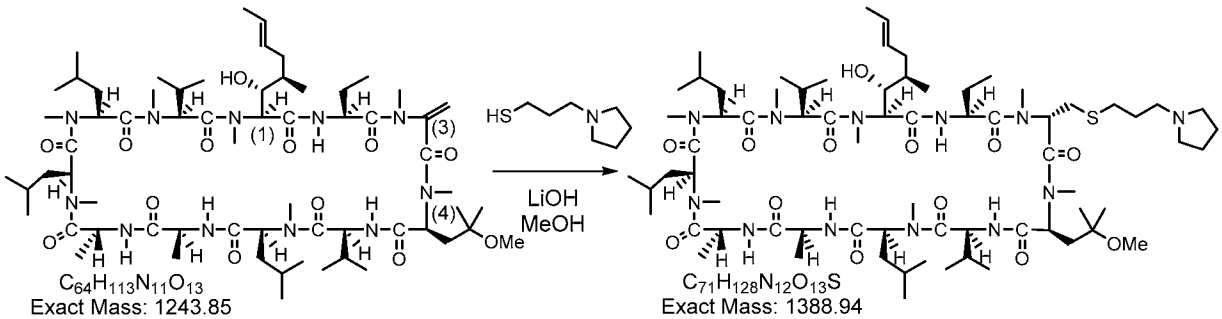


[0308] [α-Methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (0.37 g, 0.30 mmol) and 3-(N-piperidino)propylthiol (0.48 g, 3.00 mmol) were dissolved in methanol (30 ml), followed by adding 10 equivalents of lithium hydroxide (72 mg, 3.00 mmol). The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by flash chromatography using methylene chloride/methanol as eluent to give

60 mg of pure product [Molecular Formula: $C_{72}H_{130}N_{12}O_{13}S$; Exact Mass: 1402.96; MS (m/e): 1403.69 $(M+1)^+$, 1425 $(M+Na)^+$; TLC: R_f: 0.3 (ethyl acetate/methanol = 10/1); HPLC RT: 13.59 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 167

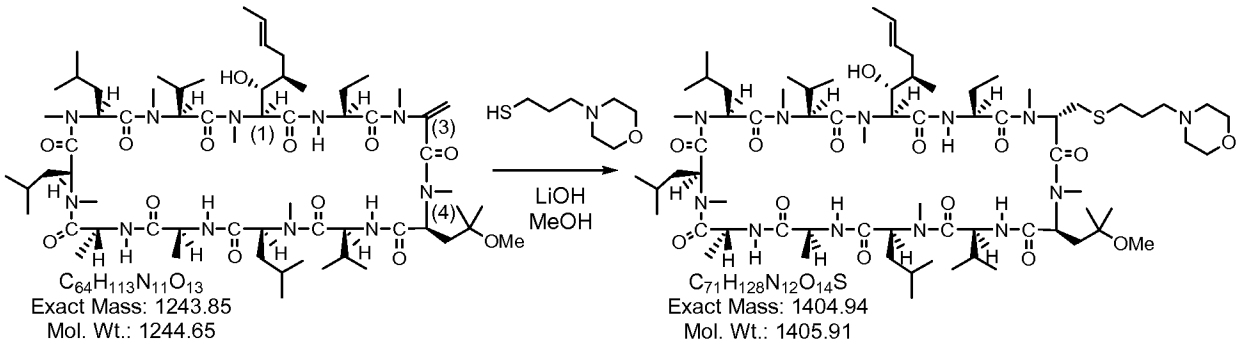
[(S)-(3-(N-Pyrrolidinyl)propylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0309] To a solution of [α-methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (280 mg, 0.23 mmol) and 3-(N-pyrrolidinyl)propanethiol (350 mg, 2.41 mmol) in methanol (15 ml) was added lithium hydroxide (120 mg, 5.00 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (80 ml) and water (25 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 94/6) to give 47 mg of product [Molecular Formula: $C_{71}H_{128}N_{12}O_{13}S$; Exact Mass: 1388.94; MS (m/z): 1389.68 $(M+1)^+$; TLC Rf: 0.30 (dichloromethane/methanol = 95/5); HPLC RT: 13.25 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 168

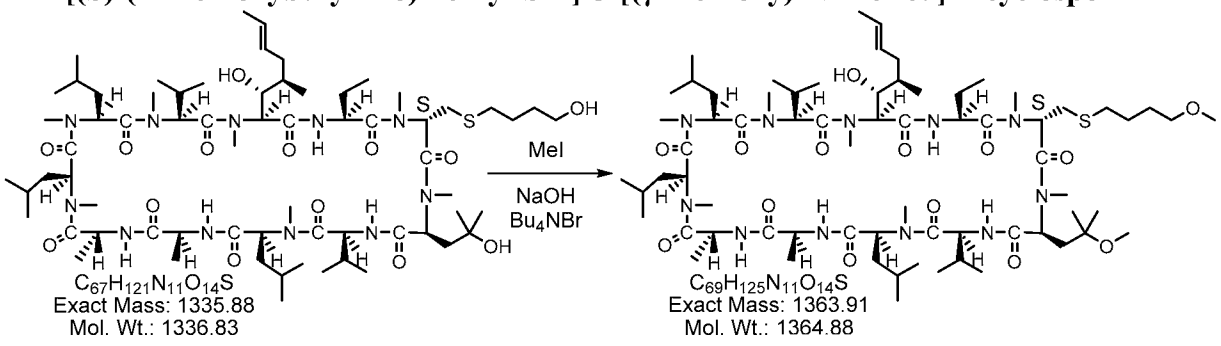
[(S)-(3-(N-Morphlino)propylthio)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0310] To a solution of [α-Methylene-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (320 mg, 0.26 mmol) and 3-morpholinopropanethiol (600 mg, 3.73 mmol) in methanol (25 ml) was added lithium hydroxide (140 mg, 5.83 mmol). The reaction mixture was stirred at room temperature overnight. Then most of solvent was evaporated under reduced pressure. Dichloromethane (60 ml) and water (25 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give 58 mg of product [Molecular Formula: $C_{71}H_{128}N_{12}O_{14}S$; Exact Mass: 1404.94; MS (m/z): 1405.52 $(M+1)^+$; TLC Rf: 0.39 (dichloromethane/methanol = 9/1); HPLC RT: 15.96 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 169

[(S)-(4-Methoxybutylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

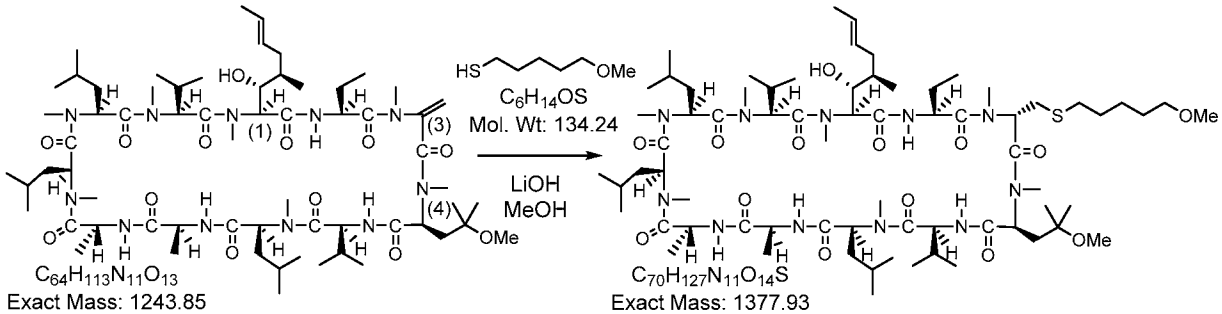


[0311] [(S)-(4-Hydroxylbutylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (100 mg, 0.075 mmol) was dissolved in of benzene (3 ml), followed by adding 3.5 equivalents of tetrabutylammonium bromide, 75 equivalents of 50 % of sodium hydroxide and iodomethene (0.425 g. 3.00 mol). The mixture was stirred overnight at room temperature and diluted with benzene (10 ml). The organic mixture was washed with brine,

dried over magnesium sulfite and evaporated under reduced pressure. The residue was subject to a flash chromatography using ethyl acetate/methanol as eluent to give 25 mg of product [Molecular formula: $C_{69}H_{125}N_{11}O_{14}S$; Exact Mass: 1363.91; MS (m/z): 1364.35$(M+1)^+$, 1386.70 $(M+Na)^+$; TLC R_f: 0.38 (ethyl acetate/methanol = 20/1); HPLC RT: 16.72 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temp: 64 °C; Detector: 210 nm)].

Example 170

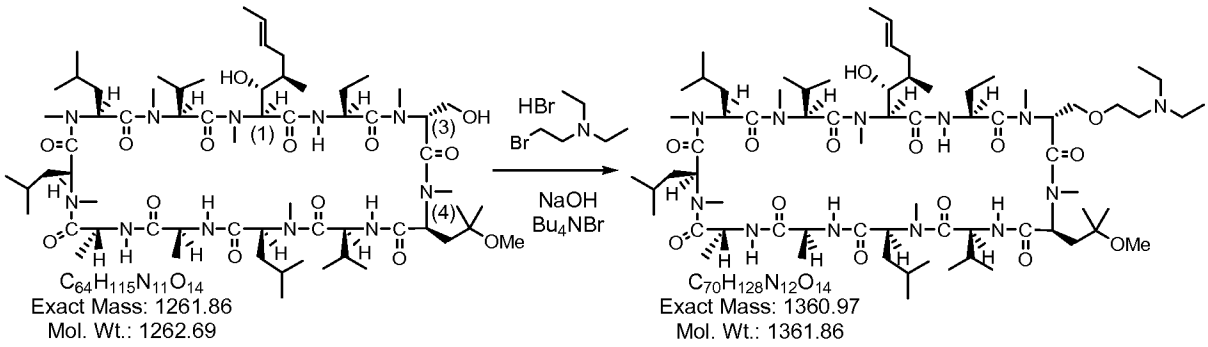
[(S)-((5-Methoxypentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin



To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (500 mg, 0.41 mmol) and 5-methoxypentanethiol (320 mg, 2.38 mmol) in methanol (15 ml) was added lithium hydroxide (100 mg, 4.17 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (hexane/acetone from 90/10 to 80/20) to give 19 mg of pure product [Molecular Formula: $C_{70}H_{127}N_{11}O_{14}S$; Exact Mass: 1377.93; MS (m/z): 1378.42 $(M+1)^+$; TLC R_f: 0.49 (hexane/acetone = 3/2); HPLC RT: 17.15 min.(C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 171

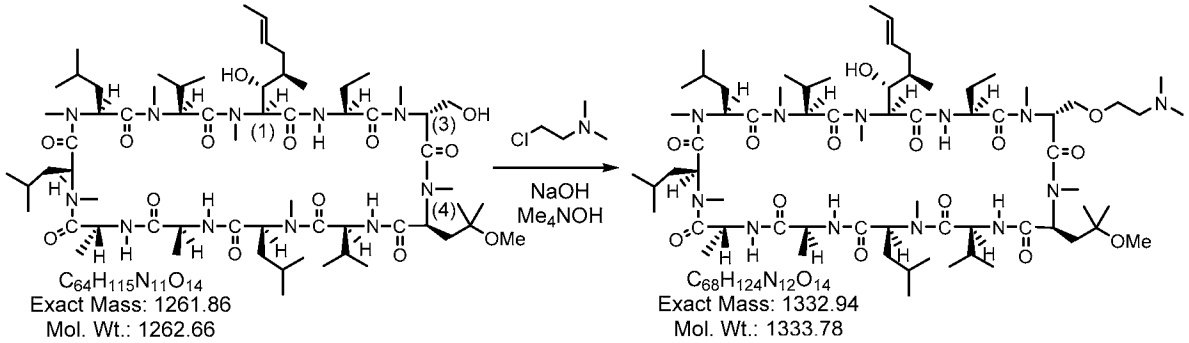
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0312] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (0.20 g, 0.16 mmol) in benzene (10 ml) were added a solution of sodium hydroxide (0.48 g, 12.00 mmol) in water (1 ml), 2-bromo-N,N-diethylethylamine hydrobromide (1.10 g, 4.21 mmol) and tetra-n-butylammonium bromide (0.10 g, 0.31 mmol). The mixture was stirred at 35 °C for 40 hours. Ice water (10 ml) was added and the mixture was separated. The aqueous layer was extracted with dichloromethane (20 ml). The combined organic layers was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 36 mg of product [Molecular Formula: $C_{70}H_{128}N_{12}O_{14}$; Exact Mass: 1360.97; MS (m/z): 1383.74 $(M+Na)^+$; TLC R_f: 0.32 (dichloromethane/methanol = 95/5); HPLC RT: 13.66 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm); ^{1}H NMR spectrum (600 MHz, $CDCl_3$, δ in ppm): 0.65(d, J = 4.8Hz, 3H), 0.82 (m, 9H), 0.87 (m, 6H), 0.91 (d, J = 6. Hz, 3H), 0.93 (d, J = 6.0Hz, 3H), 0.98-1.01 (m, 15 H), 1.07 (d, J=6.6Hz, 3H), 1.11(s, 6H), 1.23 (m, 6 H), 1.33 (d, J=7.2 Hz, 3H), 1.39-1.47 (m, 2H), 1.53-1.58 (m, 4H), 1.6 (m, 3H), 1.67-1.75 (m, 3H), 1.98-2.12 (m, 4H), 2.43-2.48 (m, 3H), 2.50-2.54 (m, 4H), 2.60 (t, J=6.0Hz, 2H), 2.67 (s, 3H), 2.68 (s, 3H), 3.07 (s, 3H), 3.10 (s, 3H), 3.12 (s, 3H), 3.24 (s, 3H), 3.26 (s, 3H), 3.48 (m, 4H), 3.52-3.56 (m, 1H), 3.60-3.62 (m, 1H), 3.67-3.70 (m, 1H), 3.80 (m, 1H), 4.06 (t, J=9.6 Hz, 1H), 4.52 (m, 1H), 4.57 (m, 1H), 4.80 (m, 1H), 4.91 (t, J=7.8Hz, 1H), 5.04 (m, 3H), 5.11 (d, J=11.4Hz, 1H), 5.28-5.34 (m, 2 H), 5.50 (d, J=7.2Hz, 1 H), 5.67 (m, 1H), 7.10 (d, J=7.8Hz 1H), 7.48 (d, J=7.80Hz,1H), 7.58 (d, J=7.2Hz,1H), 7.91 (d, J=10.2Hz,1H)].

Example 172

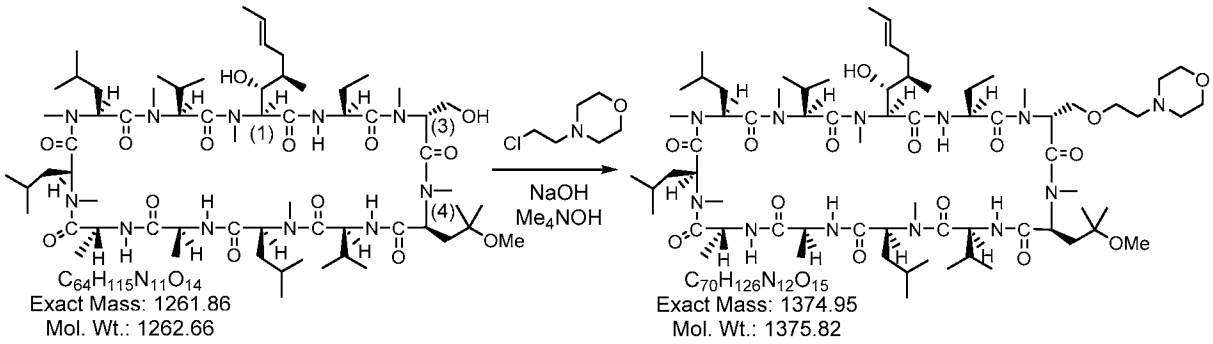
[(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0313] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.20 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 2-dimethylaminoethyl chloride hydrochloride (570 mg, 3.96 mmol). The mixture was stirred at 40 to 50 °C for two days. Sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 2-dimethylaminoethyl chloride hydrochloride (570 mg, 3.96 mmol) were added and the mixture was kept stirring at 40 to 50 °C for another two days. Another portion of 2-dimethylaminoethyl chloride hydrochloride (1.14 g, 7.91 mmol) was added and the stirring was continued at 40 to 50 °C for one more day. Sodium bicarbonate saturated solution (30 ml) was added and the mixture was separated. Then the aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 ml). The resulting ethyl acetate phase was washed with acetic acid solution (5 ml in 10 ml water) and sodium bicarbonate saturated solution (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 21 mg product was obtained [Molecular Formula: $C_{68}H_{124}N_{12}O_{14}$; Exact Mass: 1332.94; MS (m/z): 1333.75 $(M+1)^+$, 1355.87 $(M+Na)^+$; TLC R_f: 0.22 (dichloromethane/methanol = 9/1); HPLC RT: 17.3 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)]

Example 173

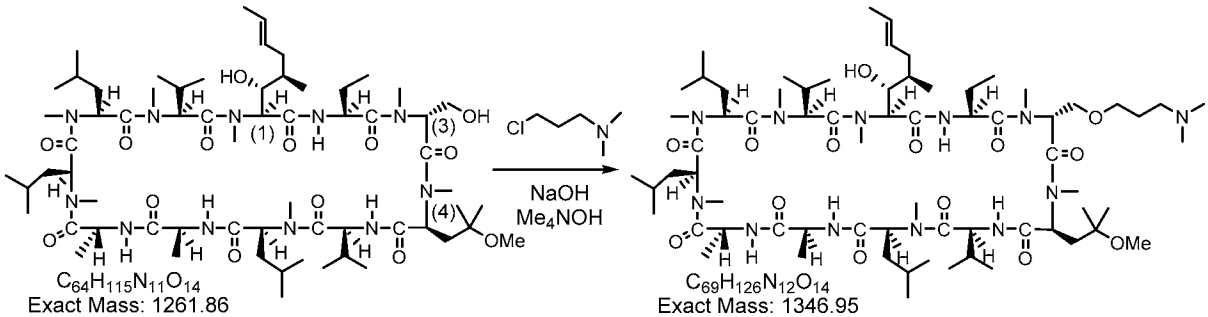
[(R)-(2-(N-Morphlino)ethoxy)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin



[0314] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.20 mmol) in benzene (20 ml) was added a solution of sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), followed by tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 2-(4-morpholinyl)ethyl chloride hydrochloride (737 mg, 3.96 mmol). The mixture was stirred at 40 to 50 °C for two days. Sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 2-(4-morpholinyl)ethyl chloride hydrochloride (737 mg, 3.96 mmol) were added and the mixture was kept stirring at 40 to 50 °C for another two days. Another portion of 2-(4-morpholinyl)ethyl chloride hydrochloride (1.47 g, 7.91 mmol) was added and the stirring was continued at 40 to 50 °C for two more days. Sodium bicarbonate saturated solution (30 ml) was added and the mixture was separated. Then the aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 ml). And the resulting ethyl acetate phase was washed with acetic acid solution (5 ml in 10 ml water) and sodium bicarbonate saturated solution (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 45 mg product was obtained [Molecular Formula: $C_{70}H_{126}N_{12}O_{15}$; Exact Mass: 1374.95; MS (m/z): 1375.63 $(M+1)^+$, 1397.79 $(M+Na)^+$; TLC R_f: 0.42 (dichloromethane/methanol = 9/1); HPLC RT: 12.9 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)]

Example 174

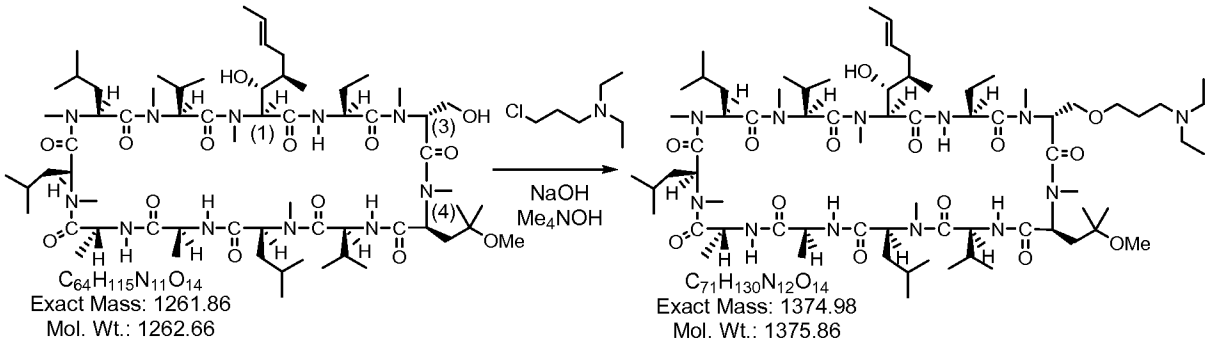
[(R)-(3-(N,N-Dimethylamino)propoxy)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporine



[0315] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.20 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 3-dimethylaminopropyl chloride hydrochloride (626 mg, 3.96 mmol). The mixture was stirred at 40 to 50 °C for two days. Sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 3-dimethylaminopropyl chloride hydrochloride (626 mg, 3.96 mmol) were added and the mixture was kept stirring at 40 to 50 °C for another two days. Another portion of 3-dimethylaminopropyl chloride hydrochloride (1.25 g, 7.91 mmol) was added and the stirring was continued at 40 to 50 °C for one more day. Sodium bicarbonate saturated solution (30 ml) was added and the mixture was separated. Then the aqueous layer was extracted with ethyl acetate (25 ml × 2). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 ml). And the resulting ethyl acetate phase was washed with acetic acid solution (5 ml in 10 ml water) and sodium bicarbonate saturated solution (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 36 mg product was obtained [Molecular Formula: $C_{69}H_{126}N_{12}O_{14}$; Exact Mass: 1346.95; MS (m/z): 1347.65 $(M+1)^+$, 1369.74 $(M+Na)^+$; TLC R_f: 0.21 (dichloromethane/methanol = 9/1). HPLC RT: 18.8 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)].

Example 175

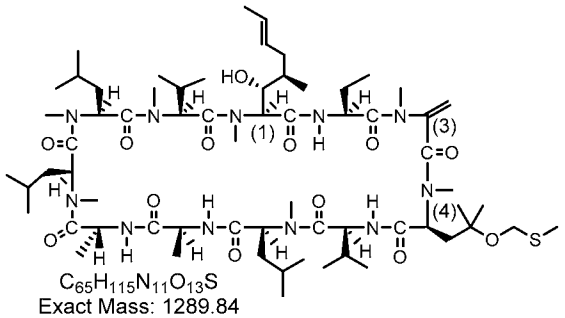
[(R)-(3-(N,N-Diethylamino)propoxy)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporine



[0316] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin (250 mg, 0.20 mmol) in benzene (20 ml) was added a solution of sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), followed by adding tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 3-diethylaminopropyl chloride hydrochloride (737 mg, 3.96 mmol). The mixture was stirred at 40 to 50 °C for two days. Sodium hydroxide (633 mg, 15.85 mmol) in water (0.70 ml), tetramethylammonium hydroxide pentahydrate (720 mg, 3.96 mmol) and 3-diethylaminopropyl chloride hydrochloride (737 mg, 3.96 mmol) were added and the mixture was kept stirring at 40 to 50 °C for another two days. Another portion of 3-diethylaminopropyl chloride hydrochloride (1.47 g, 7.91 mmol) was added and the stirring was continued at 40 to 50 °C for two more days. Sodium bicarbonate saturated solution (30 ml) was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (25 ml × 2). Then the combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 ml). And the resulting ethyl acetate phase was washed with acetic acid solution (5 ml in 10 ml water) and sodium bicarbonate saturated solution (30 ml), dried over magnesium sulfate and evaporated under reduced pressure. After purified on silica gel, 38 mg product was obtained [Molecular Formula: $C_{71}H_{130}N_{12}O_{14}$; Exact Mass: 1374.98; MS (m/z): 1375.70 $(M+1)^+$, 1397.80 $(M+Na)^+$; TLC R_f: 0.24 (dichloromethane/methanol = 9/1); HPLC RT: 19.6 min (C8 reverse phase column: 250 mm; acetonitrile/0.077% ammonium acetate in water; operation temperature: 64 °C; detector: 210 nm)]

Example 176

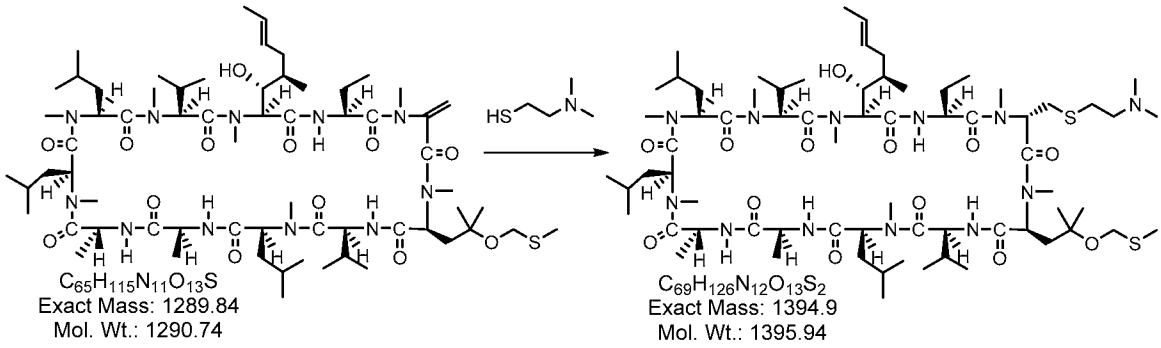
[α-Methylene-Sar]-3-[(γ-methylthiomethoxy)-NMeLeu]-4-cyclosporin



[0317] [α-Methylene-Sar]-3-[(γ-methylthiomethoxy)-N-MeLeu]-4-cyclosporin was prepared according to the method described in Example 28. The product was purified by chromatography on silica gel (ethyl acetate/methanol) [Molecular Formula: $C_{65}H_{115}N_{11}O_{13}S$; Exact Mass: 1289.84; MS (m/z): 1290.70 $(M+1)^+$, 1312.67 $(M+Na)^+$].

Example 177

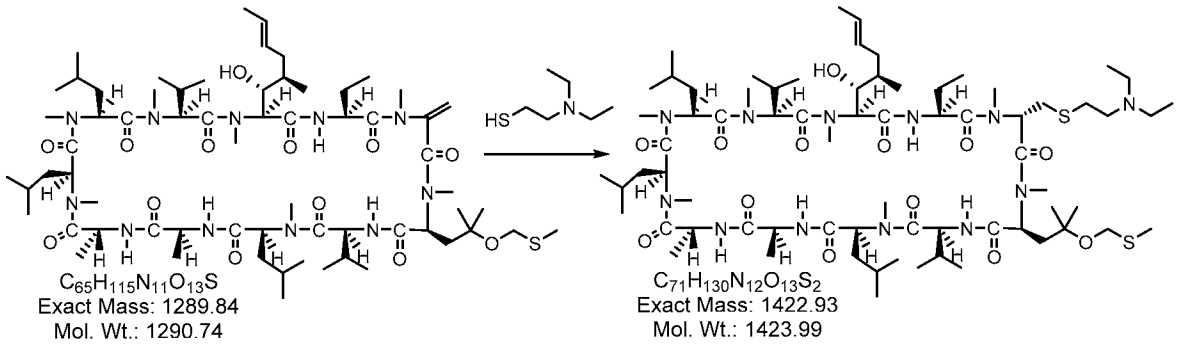
[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[(γ-methylthio)methoxy-NMeLeu]-4-cyclosporin



[0318] [α-Methylene-Sar]-3-[(γ-methylthiomethoxy)-N-MeLeu]-4-cyclosporin (0.32 g, 0.25 mmol) and 2-(N,N-dimethyl)ethanethiol (0.26 g, 2.50 mmol) were dissolved in methanol (20 ml), followed by adding 24 equivalents of triethylamine. The mixture was stirred overnight. After removal of solvent, the residue was subject to chromatography using dichloromethane/methanol as eluent to give 0.14 g of pure product [Molecular Formula, $C_{69}H_{126}N_{12}O_{13}S_2$; Exact Mass: 1394.90; MS (m/z): 1395.70 $(M+1)^+$, 1417.68 $(M+Na)^+$; TLC R_f: 0.10 (ethyl acetate/methanol = 10:1); HPLC RT: 13.30 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 178

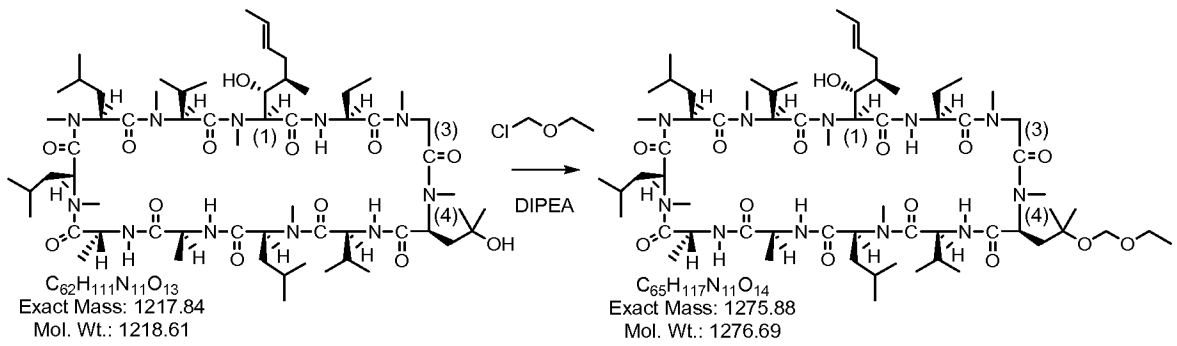
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-methylthio)methoxy-NMeLeu]-4-cyclosporin



[0319] [α-Methylene-Sar]-3-[(γ-methylthiomethoxy)-N-MeLeu]-4-cyclosporin (0.27 g, 0.21 mmol) and 2-(N,N-diethyl)ethanethiol (0.28 g, 2.10 mmol) were dissolved in methanol (20 ml), followed by adding 24 equivalents of triethylamine. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by chromatography on silica gel using dichloromethane/methanol as eluent to give 0.17 g of pure product [Molecular Formula, $C_{71}H_{130}N_{12}O_{13}S_2$; Exact Mass: 1422.93; MS(m/z): 1423.70 $(M+1)^+$, 1445.67 $(M+Na)^+$; TLC R_f: 0.35 (ethyl acetate/methanol = 10:1); HPLC RT: 13.95 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 179

[γ-Ethoxymethoxy-NMeLeu]-4-cyclosporin

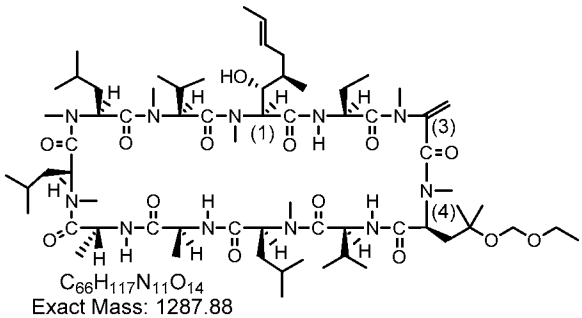


[0320] To a solution of [(γ-hydroxy)-N-MeLeu]-4-cyclosporin (1.20 g, 0.99 mmol) in dichloromethane (80 ml) was added diisopropylethylamine (FW 129.25, d 0.742, 1.32 ml, 0.98 g, 7.60 mmol), followed by adding chloromethyl ethyl ether (FW 94.54, d 1.02, 2.22 ml, 2.27 g, 24 mmol) dropwise. The mixture was stirred overnight at room temperature and TLC was used to monitor the completion of the reaction. The reaction mixture was washed

with 1 N hydrochloric acid, saturated sodium bicarbonate water solution and brine. After dried over magnesium sulfate, the mixture was evaporated under reduced pressure to give a yellowish oil, which was further purified by flash chromatography using dichloromethane/methanol as eluent to give 0.95 g of the product [Molecular Formula: $C_{65}H_{117}N_{11}O_{14}$; Exact Mass: 1275.88; MS (m/z): 1276.70 $(M+H)^+$, 1298.70 $(M+Na)^+$; TLC R_f: 0.37 (ethyl acetate)].

Example 180

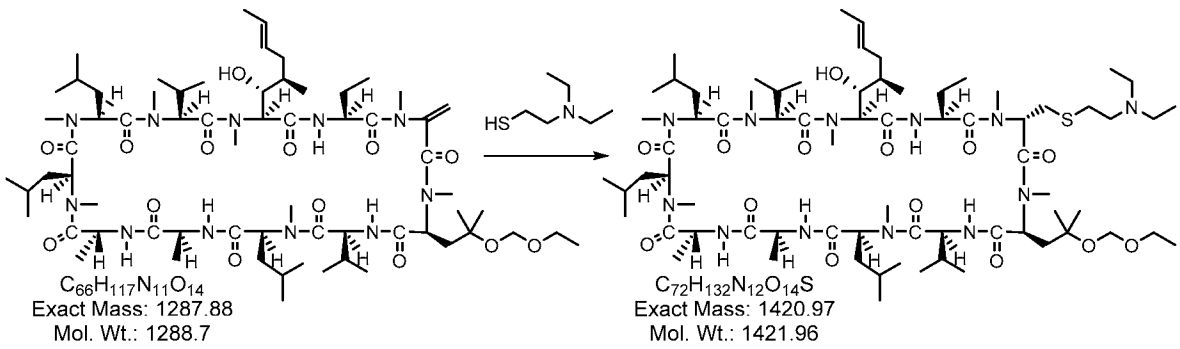
[α-Methylene-Sar]-3-[(γ-ethoxymethoxy)-NMeLeu]-4-cyclosporin



[0321] [α-Methylen-Sar]-3-[(γ-ethoxymethoxy)-N-MeLeu]-4-cyclosporin was prepared according to the method described in Example 28. The product was purified by chromatography on silica gel with ethyl acetate/methanol as eluent [Molecular Formula: $C_{66}H_{117}N_{11}O_{14}$; Exact Mass: 1287.68; MS (m/z): 1288.72 $(M+1)^+$, 1310.70 $(M + Na)^+$].

Example 181

[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-ethoxy)methoxy-NMeLeu]-4-cyclosporin

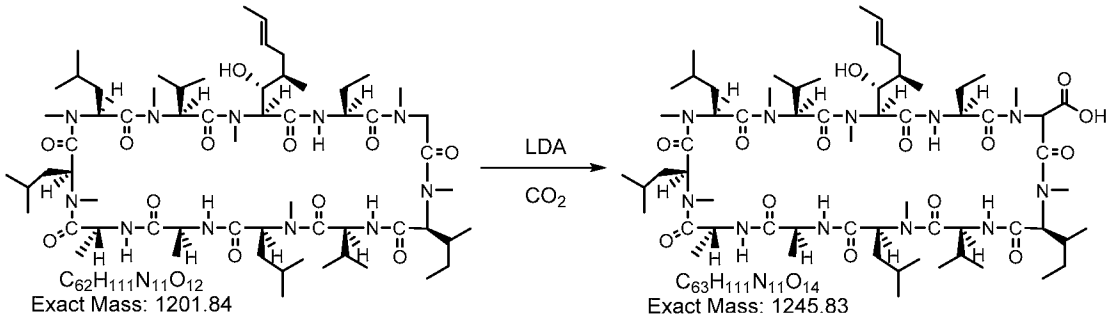


[0322] [α-Methylene-Sar]-3-[(γ-ethoxymethoxy)-N-MeLeu]-4-cyclosporin (0.27 g, 0.21 mmol) and 2-(N,N-diethyl)ethanethiol (0.28 g, 2.1 mmol) were dissolved in methanol (20 ml), followed by adding 12 equivalents of triethylamine. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by

chromatography on silica gel using dichloromethane/methanol as eluent to give 90 mg of pure product [Molecular Formula: $C_{72}H_{132}N_{12}O_{14}S$; Exact Mass: 1420.97; MS (m/z): 1421.75 $(M+1)^+$, 1443.72 $(M + Na)^+$; TLC: R_f: 0.40 (ethyl acetate/methanol = 10/1); HPLC RT: 13.58 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 182

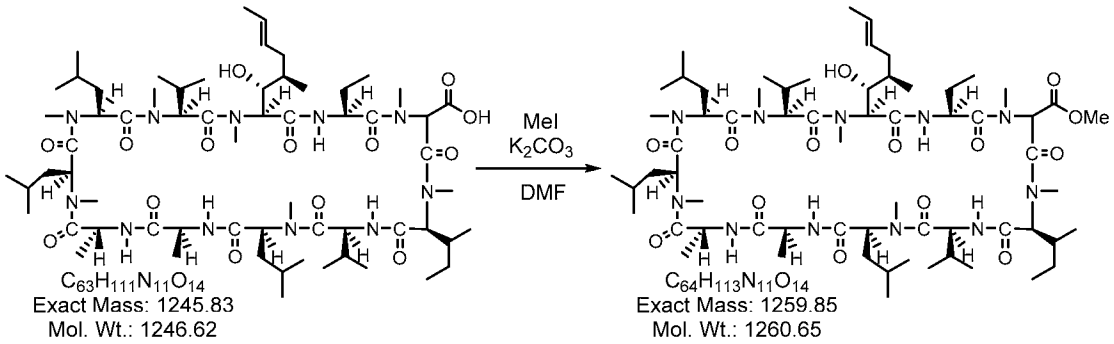
[α-Carboxy-Sar]-3-[NMeIle]-4-cyclosporin



[0323] To a solution of LDA (2.0 M in tetrahydrofuran, 5 ml, 10 mmol) in tetrahydrofuran (15 ml) at –78 °C under nitrogen atmosphere was added [N-MeIle]-4-cyclosporin (1.20 g, 1.00 mmol) in tetrahydrofuran (15 ml) over 3 min After the mixture was stirred at –78 °C for 3 hours, carbon dioxide gas was bubbled into the reaction mixture for 1 hour. Then the mixture was allowed to warm to room temperature slowly and kept stirring for another 3 hours. Most of tetrahydrofuran was evaporated under reduced pressure. Dichloromethane (100 ml) and water (50 ml) were added. The PH of the mixture was adjusted to around 5 by adding aqueous citric acid solution. The mixture was then separated and the organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 1.10 g of crude product, which was used for next step without purification [Molecular Formula: $C_{63}H_{111}N_{11}O_{14}$; Exact Mass: 1245.83; MS (m/z): 1246.68 $(M+1)^+$].

Example 183

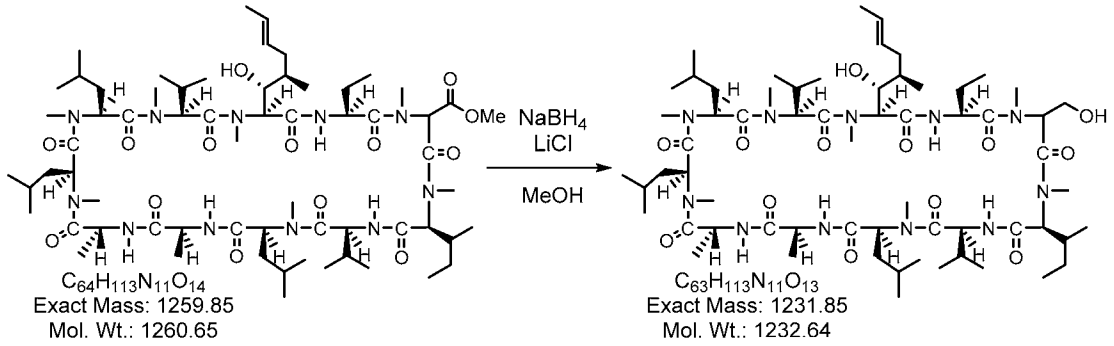
[α-Methoxycarbonyl-Sar]-3-[NMeIle]-4-cyclosporin



[0324] To a mixture of [α-carboxy-Sar]-3-[N-MeIle]-4-cyclosporin (1.00 g, 0.80 mmol) and potassium carbonate (0.70 g, 5.07 mmol) in N,N-dimethylformamide (10 ml) was added iodomethane (1.50 g, 10.56 mmol). The mixture was stirred overnight at room temperature. Dichloromethane (80 ml) and water (50 ml) were added and the mixture was separated. The dichloromethane layer was washed with water (25 ml) and brine (25 ml), dried over magnesium sulfate and evaporated under reduced pressure to give crude 1.00 g of product [Molecular Formula: $C_{64}H_{113}N_{11}O_{14}$; Exact Mass: 1259.85; MS (m/z): 1260.51$(M+1)^+$].

Example 184

[(R)-α-Hydroxymethyl-Sar]-3-[N-MeIle]-4-cyclosporin

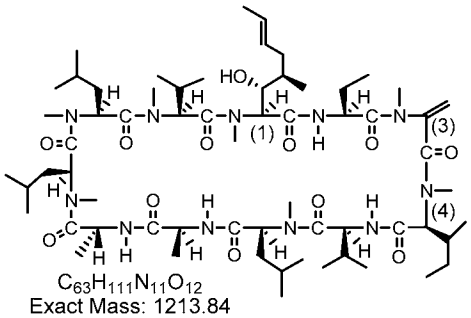


[0325] To a suspension of [α-methoxycarbonyl-Sar]-3-[N-MeIle]-4-cyclosporin (1.00 g, 0.79 mmol) and lithium chloride (0.60 g, 14.11 mmol) in methanol (80 ml) was added sodium borohydride (3.00 g, 79.26 mmol) in portions. The mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Dichloromethane (100 ml) and water (50 ml) were added and the mixture was separated. The dichloromethane layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give 420 mg of product [Molecular Formula:

$C_{63}H_{113}N_{11}O_{13}$; Exact Mass: 1231.85; MS (m/z): 1232.59 $(M+1)^+$; TLC Rf: 0.32 (dichloromethane/methanol = 95/5); HPLC RT: 14.32 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 185

[α-Methylene-Sar]-3-[NMeIle]-4-cyclosporin

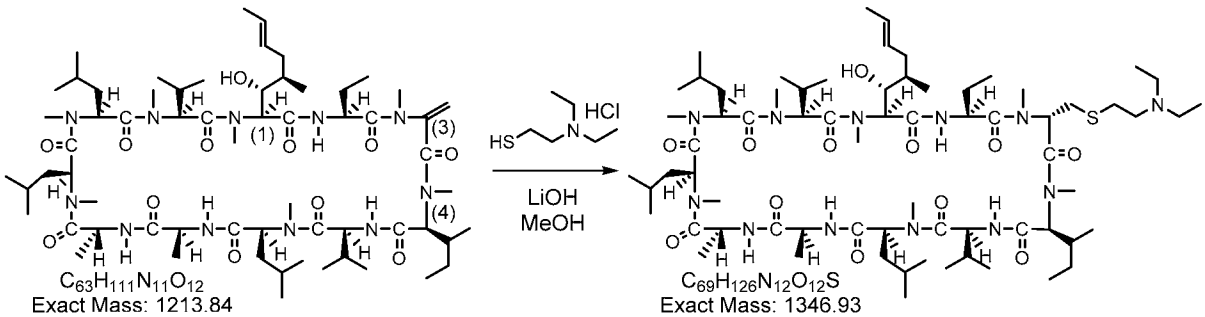


$C_{63}H_{111}N_{11}O_{12}$
Exact Mass: 1213.84
Mol. Wt.: 1214.62

[0326] [α-Methylene-Sar]-3-[N-MeIle]-4-cyclosporin was prepared according to the method described in Example 28 [Molecular Formula: $C_{63}H_{111}N_{11}O_{12}$; Exact Mass: 1213.84; MS (m/z): 1214.59 $(M+1)^+$; TLC R_f: 0.34 (hexane/acetone = 6/1); HPLC RT: 17.47 min (C8 reverse phase column: 250mm; acetonitrile/water (0.05% trifuloroacetic acid), operation temperature: 64 °C; detector: 210 nm].

Example 186

[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[NMeIle]-4-cyclosporin



$C_{63}H_{111}N_{11}O_{12}$
Exact Mass: 1213.84
Mol. Wt.: 1214.62

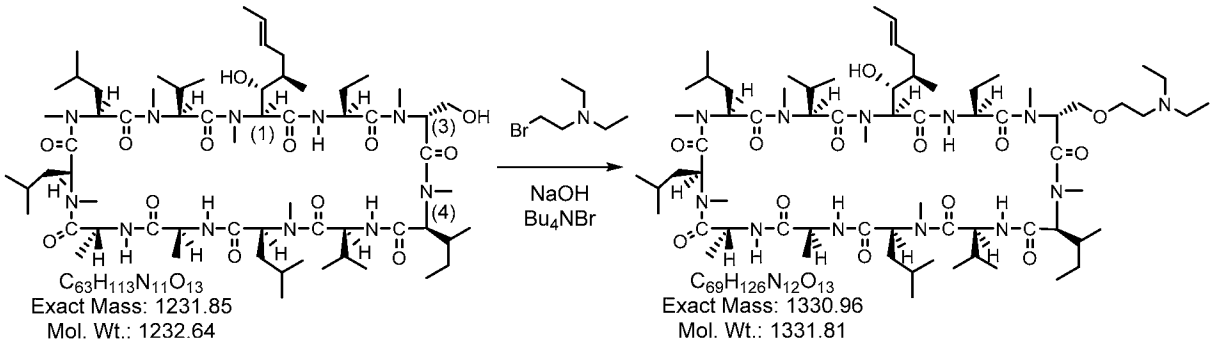
$C_{69}H_{126}N_{12}O_{12}S$
Exact Mass: 1346.93
Mol. Wt.: 1347.88

[0327] To a solution of [α-Methylene-Sar]-3-[N-MeIle]-4-cyclosporin (300 mg, 0.25 mmol) and 2-diethylaminoethanethiol hydrochloride (408 mg, 2.41 mmol) in methanol (20 ml) was added lithium hydroxide (116 mg, 4.83 mmol). The reaction mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Dichloromethane (80 ml) and water (30 ml) were added and the mixture was separated. The organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography

(dichloromethane/methanol = 96/4) to give 170 mg of product [Molecular Formula: $C_{69}H_{126}N_{12}O_{12}S$; Exact Mass: 1346.93; MS (m/z): 1347.68 $(M+1)^+$; TLC R_f: 0.32 (dichloromethane/methanol = 95/5); HPLC RT: 13.54 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 187

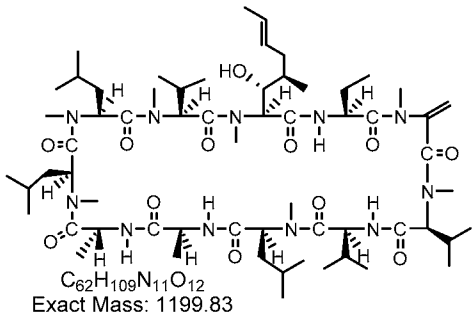
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[NMeIle]-4-cyclosporin



[0328] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[N-MeIle]-4-cyclosporin (0.39 g, 0.32 mmol) in benzene (20 ml) were added a solution of sodium hydroxide (0.80 g, 20 mmol) in water (1 ml), 2-bromo-N,N-diethylethylamine hydrobromide (2.40 g, 9.20 mmol) and tetra-n-butylammonium bromide (0.10 g, 3.10 mmol). The mixture was stirred at 30 °C for 40 hours. Ice water (10 ml) was added and the mixture was separated. The aqueous layer was extracted with dichloromethane (50 ml). The combined organic layers was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give 270 mg of product [Molecular Formula: $C_{69}H_{126}N_{12}O_{13}$; Exact Mass: 1330.96; MS (m/z): 1331.73$(M+1)^+$; TLC R_f: 0.34 (dichloromethane/methanol = 95/5); HPLC RT: 13.42 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 188

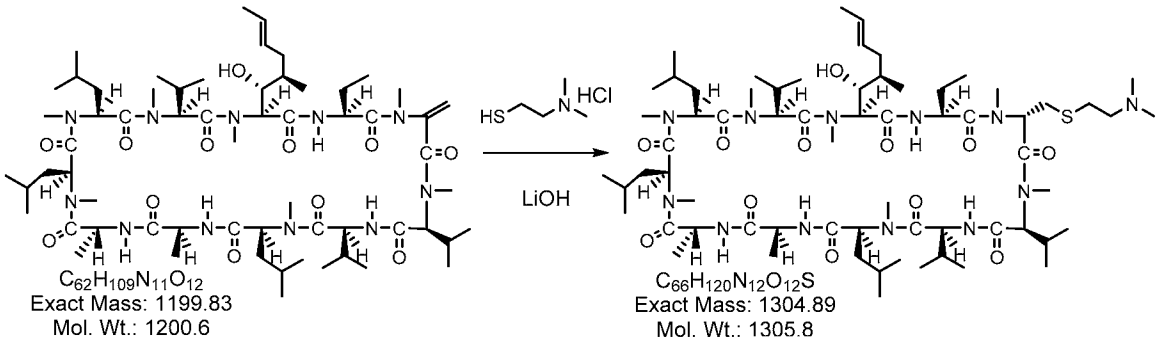
[α-Methylene-Sar]-3-[NMeVal]-4-cyclosporin



[0329] [α-Methylene]-3-[N-MeVal]-4-cyclosporin was prepared according to the method described in Example 28. The product was purified by chromatography on silica gel (ethyl acetate/methanol). [Molecular Formula: $C_{62}H_{109}N_{11}O_{12}$; Exact Mass: 1199.83; MS (m/z): 1200.56 $(M+1)^+$, 1222.72 $(M+Na)^+$].

Example 189

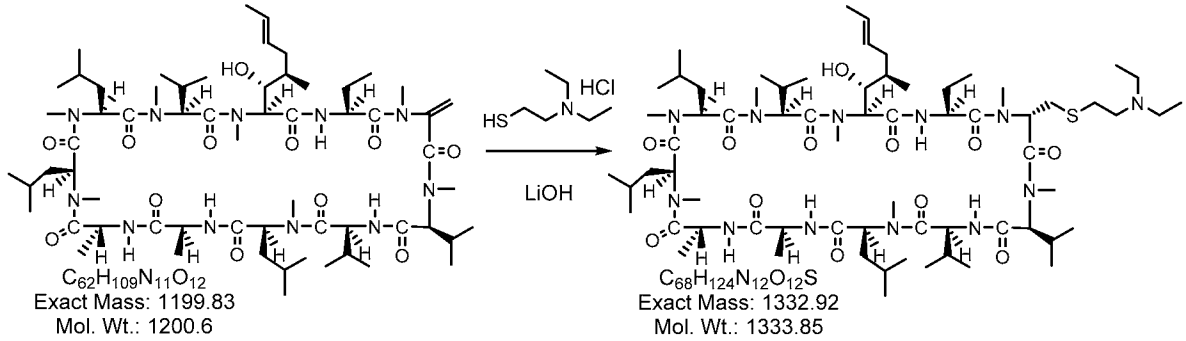
[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[NMeVal]-4-cyclosporin



[0330] [α-Methylene-Sar]-3-[N-MeVal]-4-cyclosporin (88 mg, 0.07 mmol) and 2-(N,N-dimethyl)ethanethiol hydrochloride (0.10 g, 7.30 mmol) were dissolved in methanol (20 ml), followed by adding 20 equivalents of lithium hydroxide. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was purified by flash chromatography using dichloromethane/methanol as eluent to give 30 mg of pure product [Molecular Formula: $C_{66}H_{120}N_{12}O_{12}S$; Exact Mass: 1304.89; MS (m/z): 1305.68 $(M+1)^+$, 1327.83 $(M+Na)^+$; TLC R_f: 0.05 (ethyl acetate/methanol = 5/1); HPLC RT: 12.23 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 190

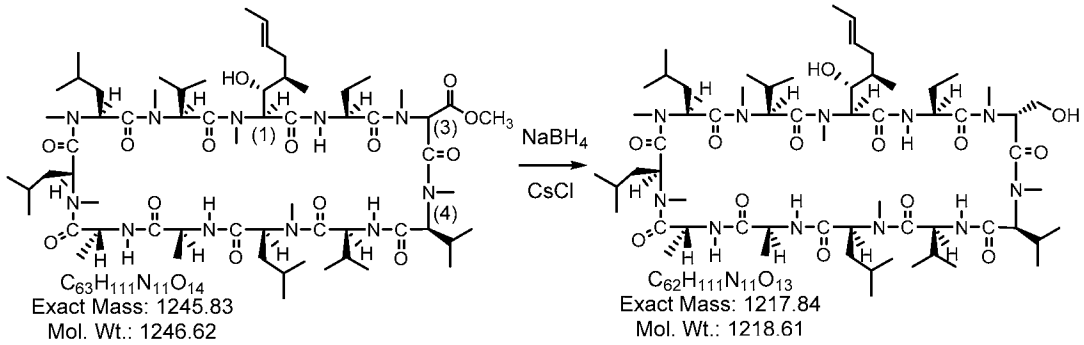
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[NMeVal]-4-cyclosporin



[0331] [α-Methylene-Sar]-3-[N-MeVal]-4-cyclosporin (0.20 g, 0.16 mmol) and 2-(N,N-9diethyl)ethanethiol hydrochloride (0.28 g, 1.70 mmol) were dissolved in methanol (20 ml), followed by adding 20 equivalents of lithium hydroxide (77 mg, 3.20 mmol). The mixture was stirred overnight. After removal of solvent, the residue was purified by chromatography on silica gel using dichloromethane/methanol as eluent to give 100 mg of pure product [Molecular Formula: $C_{68}H_{124}N_{12}O_{12}S$; Exact Mass: 1332.92; MS (m/e): 1333.58 $(M+1)^+$, 1355.79 $(M+Na)^+$; TLC R_f: 0.08 (ethyl acetate/methanol = 5/1); HPLC RT: 12.77 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 191

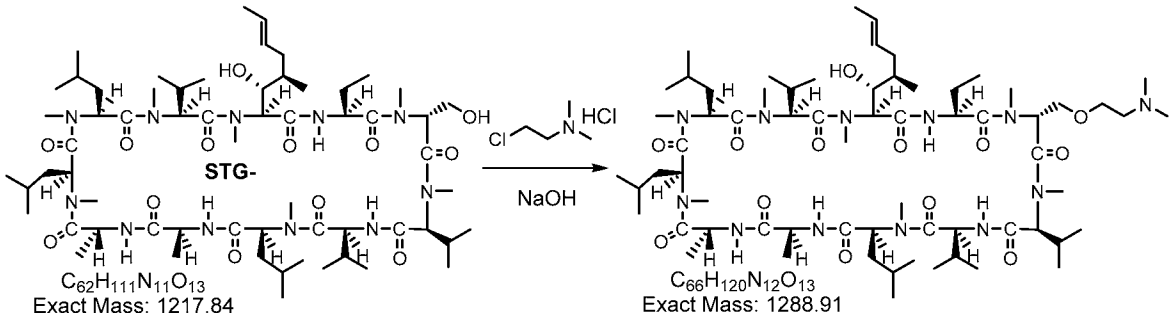
[(R)-α-Hydroxymethyl-Sar]-3-[NMeVal]-4-cyclosporin



[0332] [(R)-α-Hydroxymethyl-Sar]-3-[N-MeVal]-4-cyclosporin was prepared according to the method described in Example 2. The product was purified by chromatography on silica gel (ethyl acetate/methanol) [Molecular Formula: $C_{62}H_{111}N_{11}O_{13}$; Exact Mass: 1217.84; MS (m/z): 1218.56 $(M+1)^+$, 1240.75 $(M+Na)^+$].

Example 192

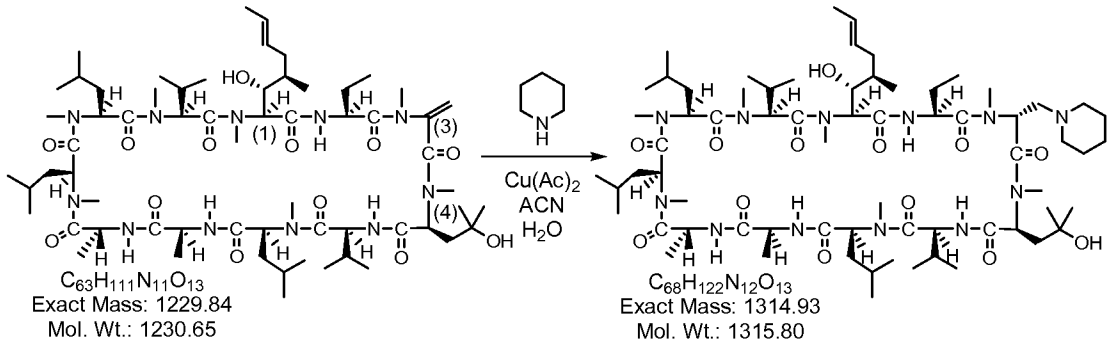
[(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-[NMeVal]-4-cyclosporin



[0333] To a solution of [(R)-α-hydroxymethyl-Sar]-3-[N-MeVal]-4-cyclosporin (0.12 g, 0.10 mmol) in benzene (15 ml) were added sodium hydroxide (0.20 g. 5.00 mmol), tetramethylammonium hydroxide pentahydrate (0.18 g, 1.00 mmol) and 3-dimethylaminoethyl chloride hydrochloride (0.14 g, 1.00 mmol). The mixture was stirred at 30 °C overnight. Ice water (20 ml) was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel (dichloromethane/methanol = 95/5) to give the 30 mg of pure product [Molecular Formula: $C_{66}H_{120}N_{12}O_{13}$; Exact Mass: 1288.91; MS (m/z): 1289.73 $(M+1)^+$, 1311.71 $(M+Na)^+$; TLC R_f : 0.14 (dichloromethane/methanol = 10/1); HPLC RT: 12.00 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 193

[(R)-(N-Piperidinyl)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin

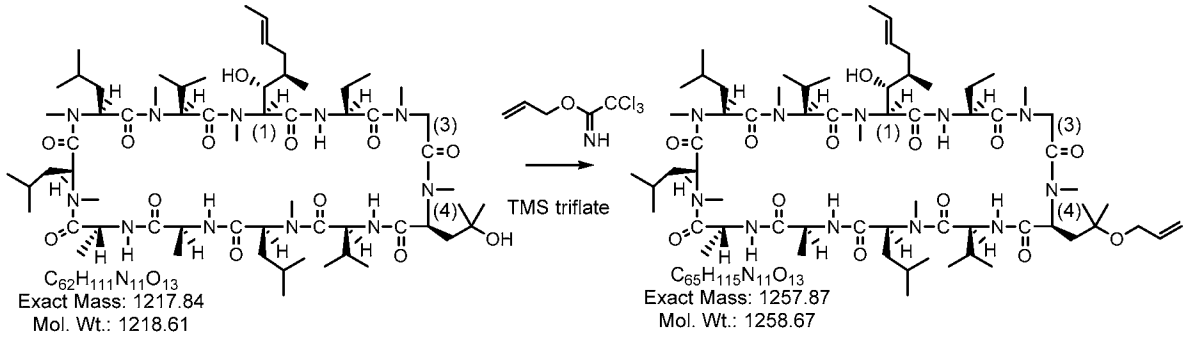


[0334] [α-Methylene-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (0.37 g, 0.30 mmol) and piperidine (0.26 g, 3.00 mmol) were dissolved in acetonitrile/water (20 ml) in the presence of the catalytic amount of copper (II) acetate. The mixture was stirred overnight at room temperature. After removal of solvent, the residue was dissolved in dichloromethane

(30 ml). The dichloromethane phase was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was further purified by chromatography on silica gel (dichloromethane/methanol, 96/4) to give 0.17 g of product [Molecular Formula: $C_{68}H_{122}N_{12}O_{13}$; Exact Mass: 1314.93; MS (m/z): 1315.74 $(M+1)^+$, 1337.86 $(M+Na)^+$; TLC R_f: 0.10 (ethyl acetate/methanol = 5/1); HPLC RT: 11.70 min (C8 reverse phase column: 150 mm; acetonitrile/water (0.05% TFA); operation temperature: 64 °C; detector: 210 nm)].

Example 194

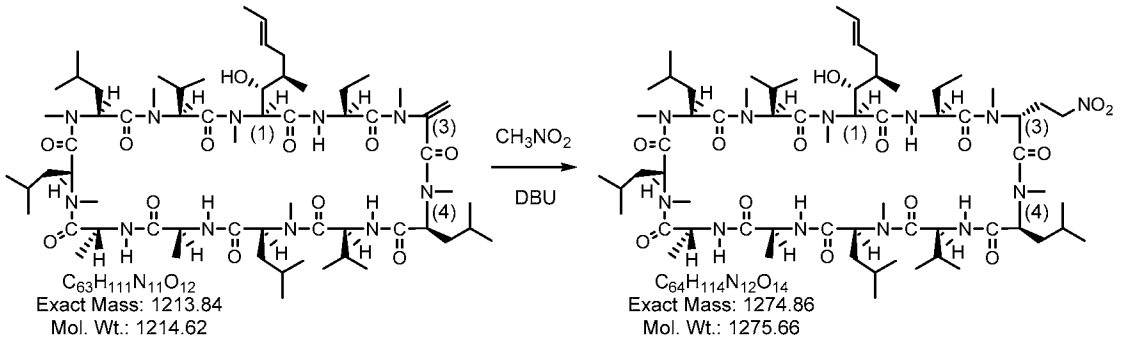
[(γ-Allyloxy)-NMeLeu]-4-cyclosporin



[0335] Under nitrogen atmosphere, to a mixture of [(γ-Hydroxy)-NMeLeu]-4-cyclosporin (FW 1218.61, 800 mg, 0.66 mmol) and ally 2,2,2-trichloroacetimidate (FW 202.47, 930 mg, 4.6 mmol) in 150 ml of DCM was added trimethylsily trifluoromethanesulfonate (FW 222.26, d 1.228, 250 mg, 1.12 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred for overnight. Then the mixture was washed with saturated $NaHCO_3$ water solution and brine. The organic layer was separated, dried over $MgSO_4$ and evaporated under vacuum. The residue was purified by column chromatography using DCM/MeOH (98/2) to give product [Molecular formula: $C_{65}H_{115}N_{11}O_{13}$; Exact Mass: 1257.87; MS (m/z): 1280.7 $(M+Na)^+$; TLC R_f: 0.46 (DCM/MeOH=95/5); HPLC RT: 16.45 minutes (C8 reverse phase column, 250 mm, acetonitrile/0.05% TFA in water, operation temperature: 64 °C; Detector: 210 nm)].

Example 195

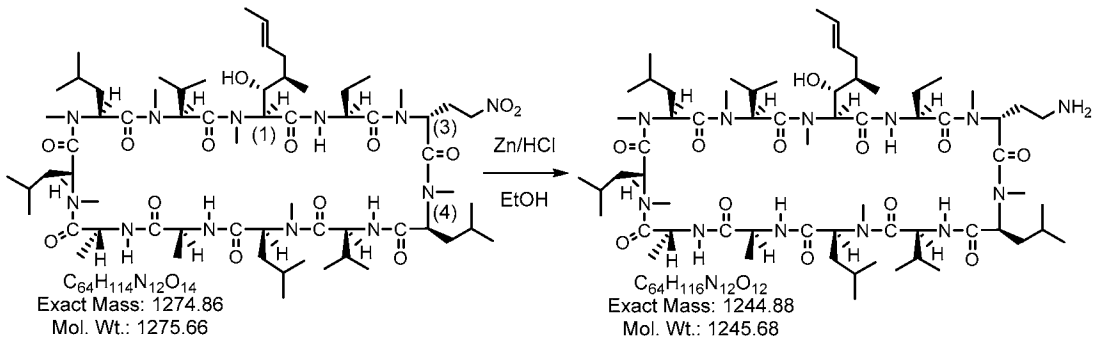
[(R)-2-Nitroethyl-Sar]-3-cyclosporin



[0336] To a solution of [α-methylene-Sar]-3-cyclosporin (FW 1214.62, 1.0 g, 0.82 mmol) in nitromethane (15 ml) was added 1,8-diazbicyclo[5,4,0]undec-7-ene (FW 152.24, 1.0 g, 6.6 mmol). After stirred at room temperature for 2 days, the reaction mixture was concentrated under reduced pressure. The residue was mixed with water dichloromethane. The dichloromethane layer was washed with aqueous citric acid solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (hexane/acetone=3/1) to give the product [Molecular formula: $C_{64}H_{114}N_{12}O_{14}$; Exact Mass: 1274.86; MS (m/z): 1275.54 $(M+1)^+$].

Example 196

[(R)-2-Aminoethyl-Sar]-3-cyclosporin

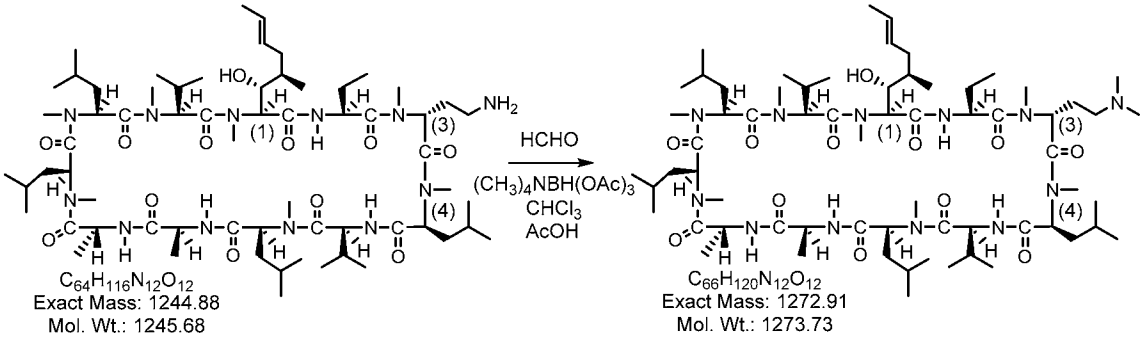


[0337] To a mixture of [(R)-2-nitroethyl-Sar]-3-cyclosporin (FW 1275.66, 210 mg, 0.16 mmol) and zinc (FW 65.38, 1 g, 15.3 mmol) in ethanol (20 ml) was added 10% aqueous hydrochloric acid (10 ml). The reaction mixture was stirred at room temperature overnight (monitored by LC-MS) and filtered. The filter cake was washed with ethanol. The filtrate was concentrated and diluted with dichloromethane. The dichloromethan layer was washed with aqueous saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by

chromatography (dichloromethane /methanol = 95/5) to give the product [Molecular formula: $C_{64}H_{116}N_{12}O_{12}$; Exact Mass: 1244.88; MS (m/z): 1245.54 $(M+1)^+$].

Example 197

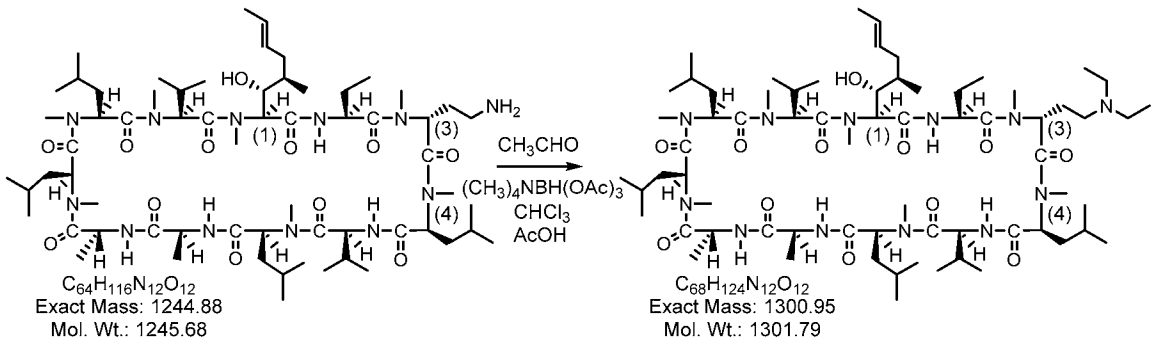
[(R)-2-(N, N-Dimethylamino)ethyl-Sar]-3-Cyclosporin



[0338] To a solution of [(R)-2-aminoethyl-Sar]-3-Cyclosporin (FW 1245.68, 122 mg, 0.1 mmol) in chloroform (6 ml) were added formaldehyde aqueous 37% solution (0.6ml) and acetic acid (6 drops). The reaction mixture was stirred at room temperature for 5 min. Then tetramethylammonium triacetoxyborohydride (FW 263.10, 131 mg, 0.5 mmol) was added and the reaction mixture was continued to stir for one hour. The mixture was diluted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 96/4) to give the product [Molecular formula: $C_{66}H_{120}N_{12}O_{12}$; Exact Mass: 1272.91; MS (m/z): 1273.70 $(M+1)^+$; TLC R_f: 0.27 (dichloromethane/methanol); HPLC RT: 12.42 minutes].

Example 198

[(R)-2-(N, N-Diethylamino)ethyl-Sar]-3-Cyclosporin

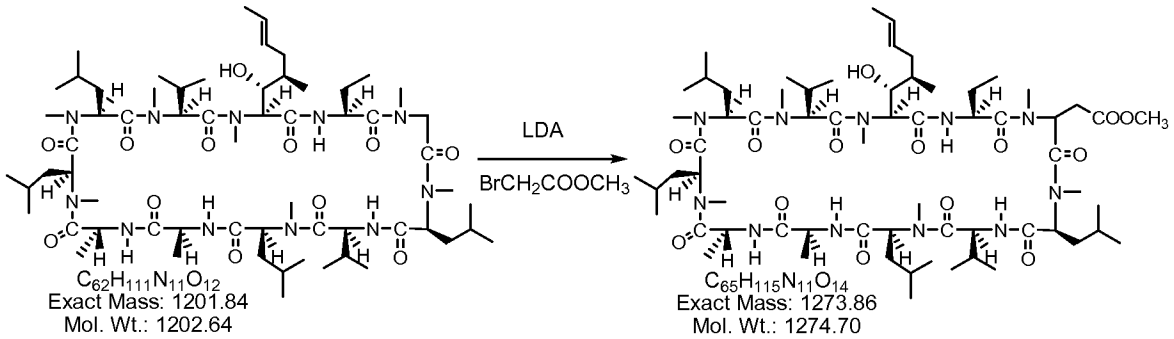


[0339] To a solution of 3-amino cyclosporine (FW 1245.68, 124 mg, 0.1 mmol) in chloroform (6 ml) were added acetaldehyde (FW 44.06, 78 mg, 1.77 mmol) and acetic acid

(drops). The reaction mixture was stirred at room temperature for 5 min. Then tetramethylammonium triacetoxyborohydride (FW 263.10, 126 mg, 0.48 mmol) was added and the reaction mixture was continued to stir for 1 hour. The mixture was diluted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give product [Molecular formula: $C_{68}H_{124}N_{12}O_{12}$; Exact Mass: 1300.95; MS (m/z): 1301.72 $(M+1)^+$; TLC R_f: 0.33 (dichloromethane/methanol = 95/5); HPLC RT: 13.28 minutes (C8 reverse phase column, 250 mm, acetonitril-water/(0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 199

[(2-Methoxy-2-oxoethyl)-Sar]-3-cyclosporin

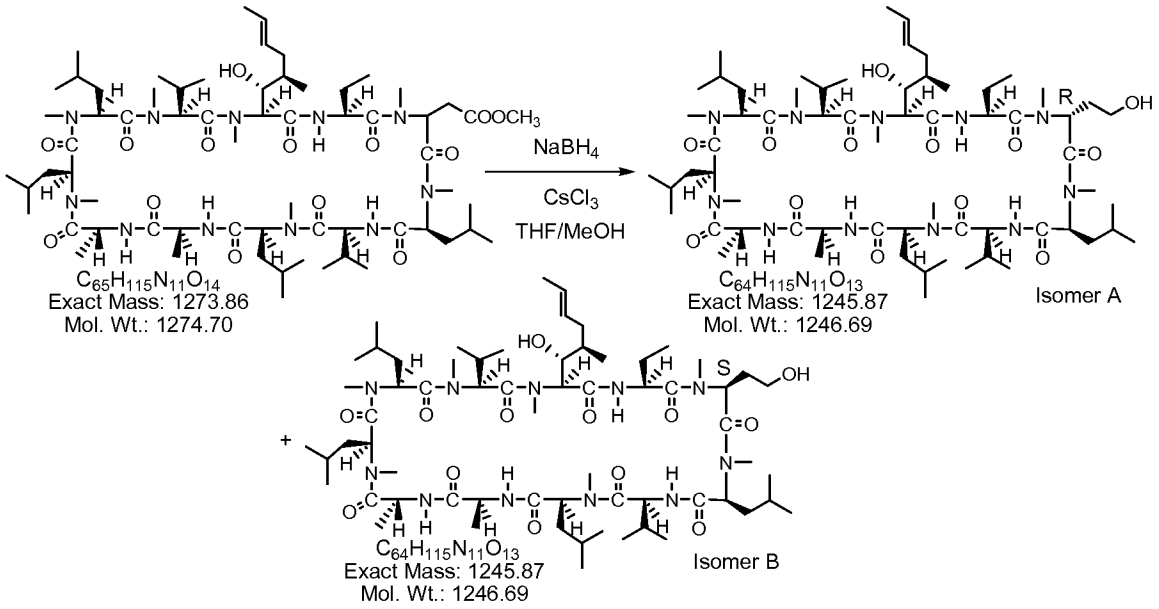


[0340] n-Butyllithium (15.84 ml, 2.89 M, 45.79 mmol) was added to a solution of diisopropylamine (6.50 ml, 45.79 mmol) in tetrahydrofuran (80 ml) at –78 °C under nitrogen and the reaction mixture was stirred for an hour. A solution of cyclosporine A (5.00 g, 4.16 mmol) in tetrahydrofuran (20 ml) was added over 10 minutes and the mixture was stirred at –78 °C for another two hours. Then methyl bromoacetate (7.00 g, 45.79 mmol) and the reaction mixture was stirred at –78 °C for one hour. The reaction mixture was allowed to warm up to room temperature slowly and stirred overnight. Most of tetrahydrofuran was removed under vacuum at room temperature. Ethyl acetate (50 ml) and 50 ml brine were added and separated. The aqueous layer was extracted with ethyl acetate (20 ml × 3). The combined ethyl acetate layers were dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column to give to give 2.11 g of [(2-methoxy-2-oxoethyl)-Sar]-3-cyclosporin [Molecular Formula: $C_{65}H_{115}N_{11}O_{14}$; Exact Mass: 1273.86; MS (m/z): 1274.44 $(M+1)^+$, 1296.63 $(M+Na)^+$].

[0341] [(2-(t-Butoxy)-2-oxoethyl)-Sar]-3-cyclosporin was synthesized using a method analogous to a procedure described by Seebach D, et al., 1993, *Helv Chim Acta,* 76, 1564-1590; which is incorporated herein by reference.

Example 200

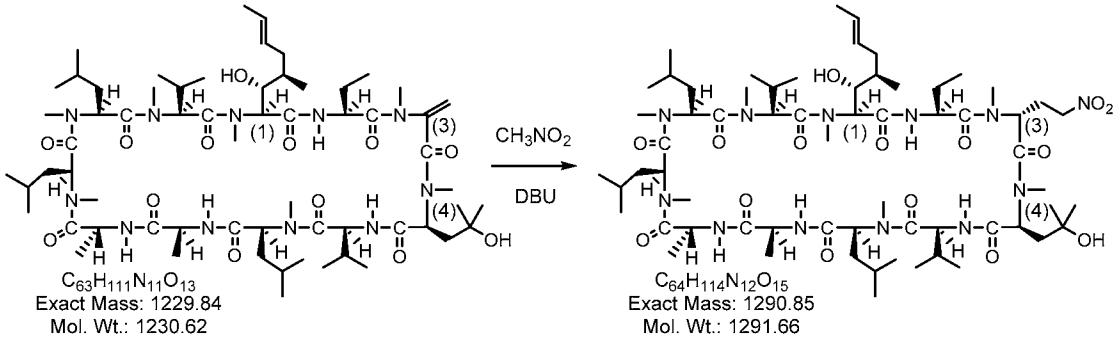
[(R)-(2-Hydroxyethyl)-Sar]-3-cyclosporin and [(S)-(2-hydroxyethyl)-Sar]-3-cyclosporin



[0342] [(2-Methoxy-2-oxoethyl)-Sar]-3-cyclosporin (1.00 g, 0.79 mmol) was dissolved in tetrahydrofuran (30 ml), followed by adding cesium chloride (1.00 g, 5.94 mmol) and sodium borohydride (1.00 g, 26.43 mmol). Then 30 ml of methanol was added dropwise to the mixture over one hour. After addition, the mixture was stirred at room temperature for another hour. Most solvent was then evaporated under reduced pressure. Ethyl acetate (30 ml) and water (30 ml) were added. The ethyl acetate layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography to give the product of isomer A as [(R)-(2-hydroxyethyl)-Sar]-3-cyclosporin [Molecular Formula: $C_{64}H_{115}N_{11}O_{13}$; Exact Mass: 1245.87; MS (m/z): 1246.49.52 $(M+1)^+$, 1268.72 $(M+Na)^+$; TLC R_f: 0.46 (dichloromethane/methanol = 9:1); HPLC RT: 16.06 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)] and the product of isomer B as [(S)-(2-hydroxyethyl)-Sar]-3-cyclosporin [Molecular Formula: $C_{64}H_{115}N_{11}O_{13}$; Exact Mass: 1245.87; MS (m/z): 1246.49 $(M+1)^+$, 1268.68 $(M+Na)^+$; TLC R_f: 0.46 (dichloromethane/methanol = 9:1); HPLC RT: 15.15 min (C8 reverse phase column: 250 mm; acetonitrile/water (0.05% trifluoroacetic acid); operation temperature: 64 °C; detector: 210 nm)].

Example 201

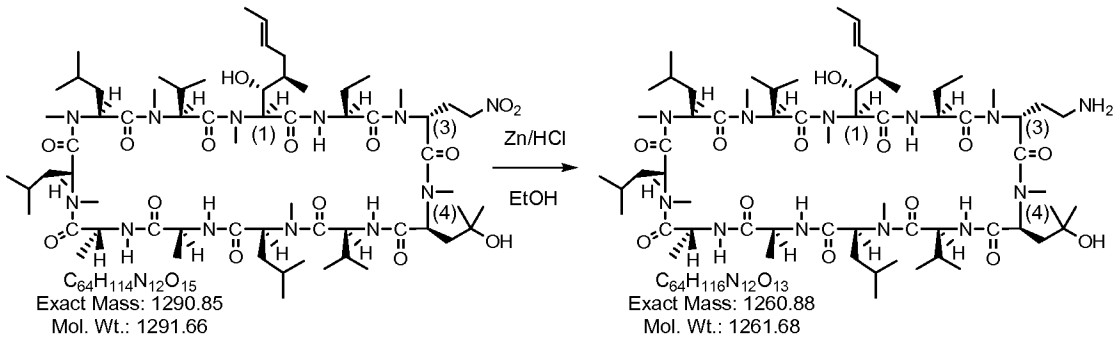
[(R)-2-Nitroethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-Cyclosporin



[0343] To a solution of [α-Methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (FW 1230.62, 1.6 g, 1.3 mmol) in 20 ml of nitromethane was added 1,8-diazbicyclo[5,4,0]undec-7-ene (4ml). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was mixed with water and dichloromethane and separated. The organic layer was washed with aqueous citric acid solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give the product (R-isomer) 600mg [Molecular formula: $C_{64}H_{114}N_{12}O_{15}$; Exact Mass: 1290.85; MS (m/z): 1291.72$(M+1)^+$. HPLC RT: 14.95 minutes]. (S-isomer) 360 mg [Molecular formula: $C_{64}H_{114}N_{12}O_{15}$; Exact Mass: 1290.85; MS (m/z): 1291.72 $(M+1)^+$; HPLC RT: 14.43 minutes].

Example 202

[(R)-2-Aminoethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-Cyclosporin

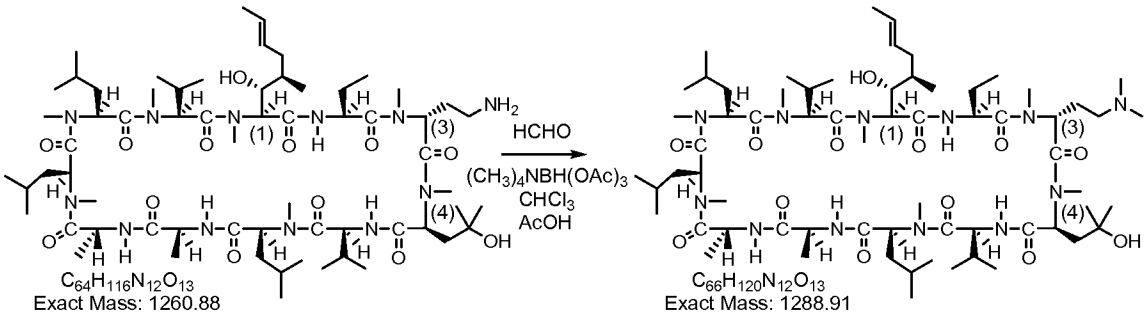


[0344] To a mixture of [(R)-2-nitroethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (FW 1291.66, 400 mg, 0.31 mmol) and zinc (1.5 g) in ethanol (30ml) was added 10% aqueous hydrochloric acid (30 ml). The reaction mixture was stirred at room temperature overnight (monitored by LC-MS) and filtered. The filter cake was washed with ethanol. The combined filtrate was concentrated and diluted with dichloromethane. The organic

layer was washed with aqueous saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 95/5) to give the product [Molecular formula: $C_{64}H_{116}N_{12}O_{13}$; Exact Mass: 1260.88; MS (m/z): 1261.70 $(M+1)^+$].

Example 203

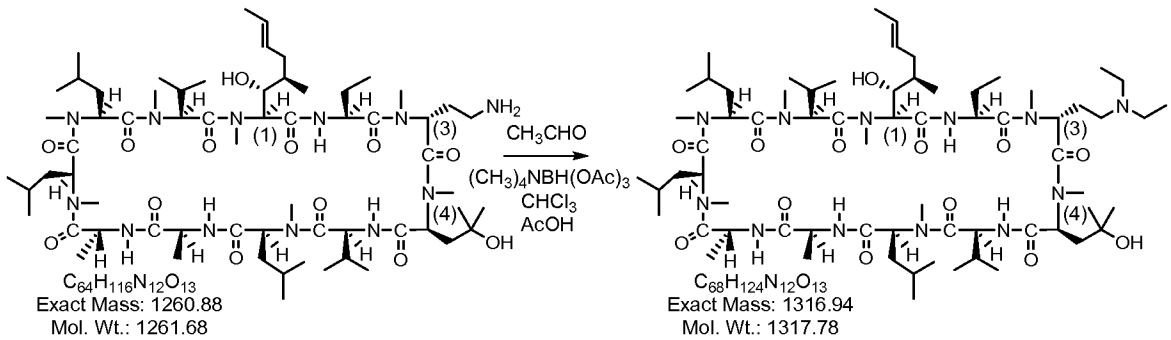
[(R)-2-(N,N-Dimethylamino)ethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0345] To a solution of [(R)-2-aminoethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (FW 1261.68, 180 mg, 0.14 mmol) in chloroform (6 ml) were added formaldehyde aqueous 37% solution (0.8 ml) and acetic acid (8 drops). The reaction mixture was stirred at room temperature for 5 min. Then tetramethylammonium triacetoxyborohydride (263.10, 200 mg, 0.76 mmol) was added and the reaction mixture was continued to stir for one hour. The mixture was diluted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 95/5) to give the product [Molecular formula: $C_{66}H_{120}N_{12}O_{13}$; Exact Mass: 1288.91; MS (m/z): 1289.76 $(M+1)^+$; TLC R_f: 0.32 (dichloromethane/methanol =9/1); HPLC RT: 11.14 minutes].

Example 204

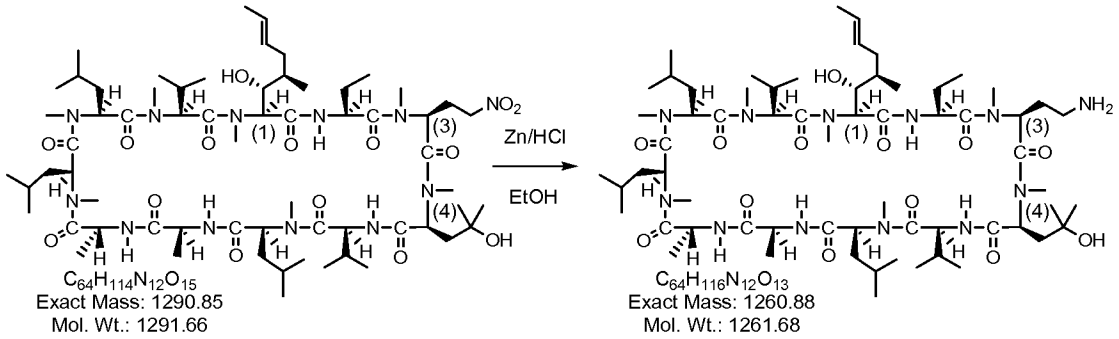
[(R)-2-(N,N-Diethylamino)ethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-Cyclosporin



[0346] To a solution of [(R)-2-aminoethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (FW 1261.68, 129 mg, 0.10 mmol) in chloroform (10 ml) were added acetaldehyde (FW 44.06, 80 mg, 1.8 mmol) and acetic acid (7 drops). The reaction mixture was stirred at room temperature for 5 min. Then tetramethylammonium triacetoxyborohydride (FW 263.10, 200 mg, 0.76 mmol) was added and the reaction mixture was continued to stir for one hour. The mixture was diluted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 95/5) to give the product [Molecular formula: $C_{68}H_{124}N_{12}O_{13}$; Exact Mass: 1316.94; MS (m/z): 1317.70 $(M+1)^+$; TLC R_f: 0.39 (Dichloromethane/methanol =9/1); HPLC RT: 12.06 minutes].

Example 205

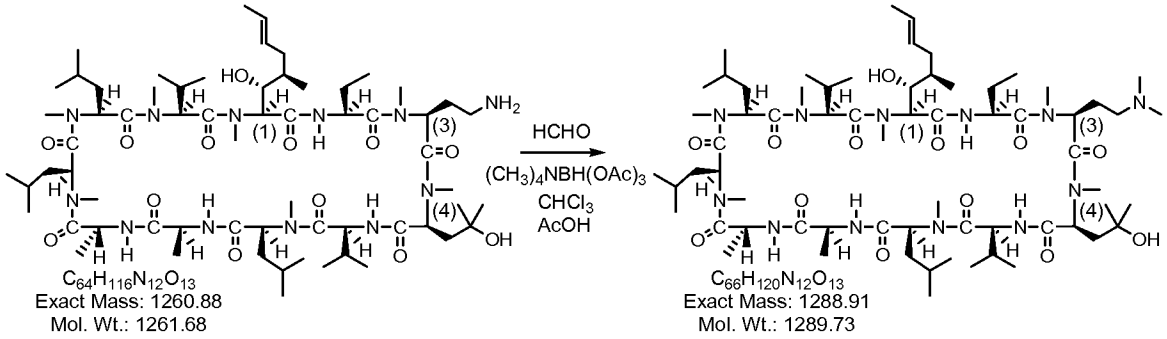
[(S)-2-Aminoethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin



[0347] To a mixture of [(S)-2-nitroethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (FW 1291.66, 350 mg, 0.27 mmol) and zinc (1.5 g) in ethanol (25 ml) was added 10% aqueous hydrochloric acid (15 ml). The reaction mixture was stirred at room temperature overnight (monitored by LC-MS) and filtered. The filter cake was washed with ethanol. The combined filtrate was concentrated and diluted with dichloromethane. The organic solution was washed with aqueous saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane /methanol=96/4) to give the product [Molecular formula: $C_{64}H_{116}N_{12}O_{13}$; Exact Mass: 1260.88; MS (m/z): 1261.64 $(M+1)^+$].

Example 206

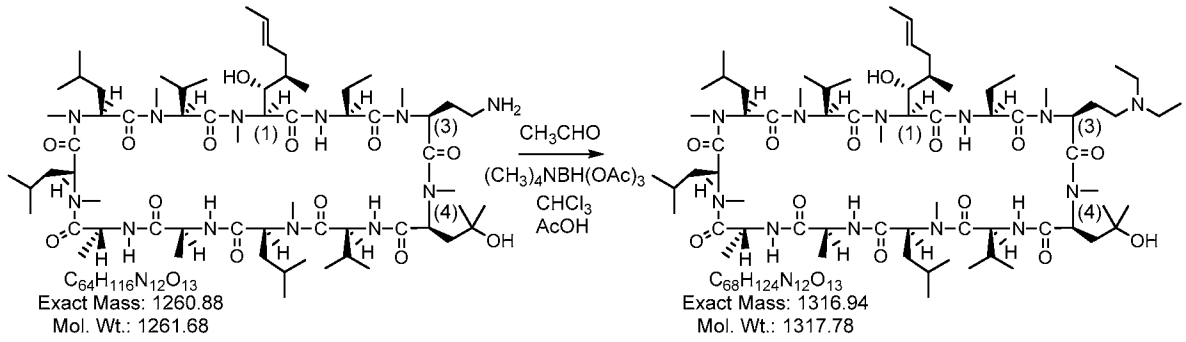
[(S)-2-(N,N-Dimethylamino)ethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-Cyclosporin



[0348] To a solution of [(S)-2-aminoethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (FW 1261.68, 13 0mg, 0.10 mmol) in chloroform (10 ml) were added formaldehyde aqueous 37% solution (0.7 ml) and acetic acid (7 drops). The reaction mixture was stirred at room temperature for 5 min. Then tetramethylammonium triacetoxyborohydride (263.10, 200 mg, 0.76 mmol) was added and the reaction mixture was continued to stir for one hour. The mixture was diluted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate solution and brine, dried over Magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 95/5) to give the product [Molecular formula: $C_{66}H_{120}N_{12}O_{13}$; Exact Mass: 1288.91; MS (m/z): 1289.70 $(M+1)^+$; TLC R_f: 0.35 (Dichloromethane/methanol =9/1); HPLC RT: 11.02 minutes].

Example 207

[(S)-2-(N,N-Diethylamino)ethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-Cyclosporin

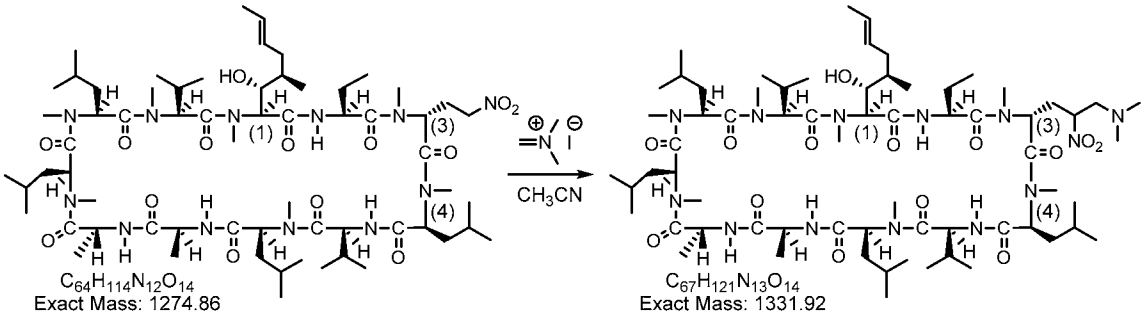


[0349] To a solution of [(S)-2-aminoethyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (FW 1261.68, 129 mg, 0.10 mmol) in chloroform (10 ml) were added acetaldehyde (FW 44.06, 80 mg, 1.8 mmol) and acetic acid (7 drops). The reaction mixture was stirred at room temperature for 5 minutes. Then tetramethylammonium triacetoxyborohydride (FW 263.10, 200 mg, 0.76 mmol) was added and the reaction mixture was continued to stir for

one hour. The mixture was diluted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol =95/5) to give the product [Molecular formula: $C_{68}H_{124}N_{12}O_{13}$; Exact Mass: 1316.94; MS (m/z): 1317.70 $(M+1)^+$; TLC R_f: 0.41 (Dichloromethane/methanol =9/1); HPLC RT: 11.96 minutes].

Example 208

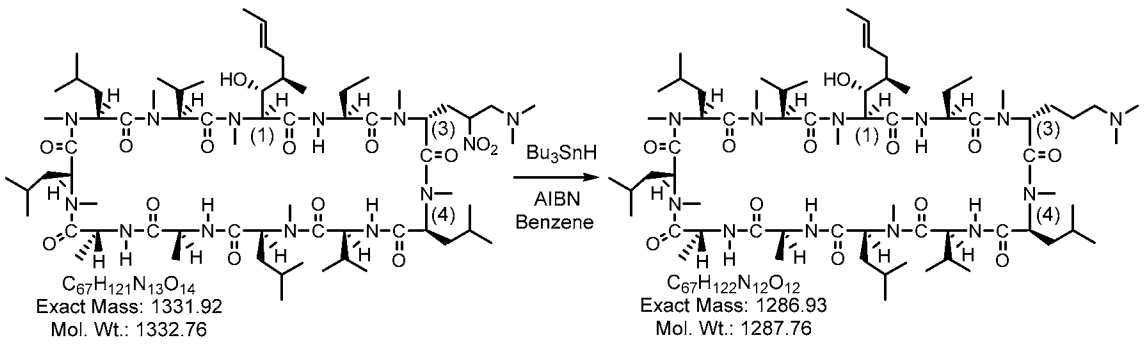
[(R)-2-Nitro-3-(N,N-Dimethylamino)propyl-Sar]-3-Cyclosporin



[0350] To a mixture of [(R)-2-nitroethyl-Sar]-3-cyclosporin (FW 1275.66, 360 mg, 0.28 mmol) and dimethymethyleneammonium iodide (FW 185.01, 550 mg, 15.4 mmol) acetonitrile (in 25 ml) was added triethylamine (10 drops). The reaction mixture was stirred at room temperature overnight (monitored by LC-MS). The mixture was concentrated and diluted with dichloromethane. The organic layer was washed with aqueous water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was used for next step.

Example 209

[(R)-3-(N,N-Dimethylamino)propyl-Sar]-3-Cyclosporin

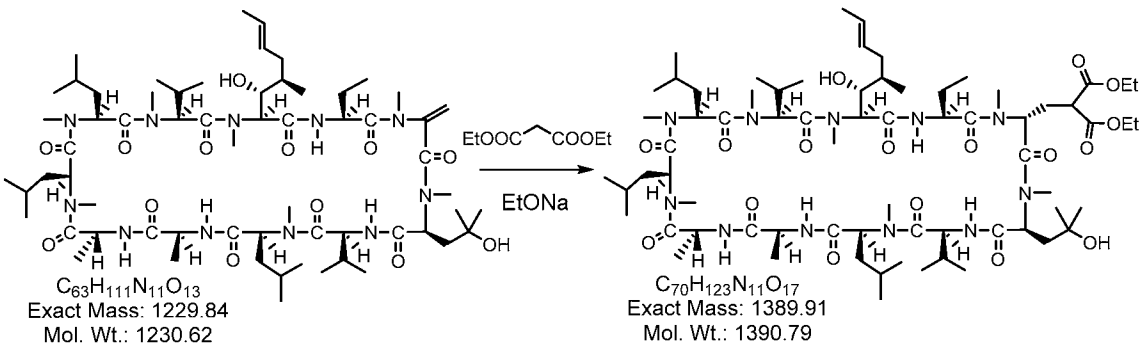


[0351] To a mixture of cylcosporine (crude form previous step FW 1332.76, 0.28 mmol) and tri-n-butyltin hydride (FW 291.07, 0.41 g, 1.4 mmol) in benzene (25 ml) was

added AIBN (FW 164.21, 46 mg, 0.28 mmol) under nitrogen atmosphere. The mixture was heated to reflux with stirring for 8 hours. After the reaction was completed (monitored by LC-MS), the reaction mixture was washed with aqueous saturated sodium bicarbonate solution and brine followed by evaporated under vacuum. The residue was purified by chromatography (Dichloromethane/methanol = 95/5) to give the product [Molecular formula: $C_{67}H_{122}N_{12}O_{12}$; Exact Mass: 1286.93; MS (m/z): 1287.71 $(M+1)^+$; TLC R_f: 0.36 (dichloromethane/methanol =95/5); HPLC RT: 12.57 minutes].

Example 210

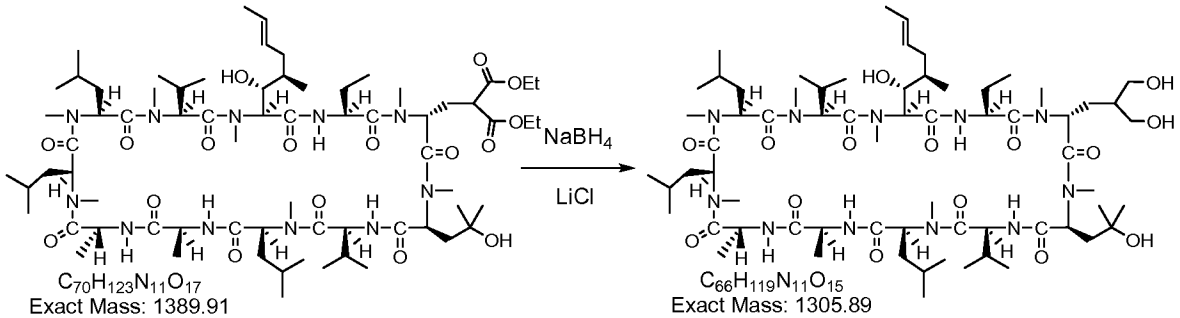
[(R)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[0352] To a solution of [α-methylene-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (0.61 g, 0.50 mmol) and diethyl malonate (1.00 g, 6.25 mmol) in ethanol anhydrous (30 ml) was added sodium ethoxide (0.82 g, 12.05 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was mixed with water (30 ml) and dichloromethane (80 ml) and separated. The organic layer was washed with aqueous citric acid and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography (hexane/acetone = 2/1) to give the product. [Molecular formula: $C_{70}H_{123}N_{11}O_{17}$; Exact Mass: 1389.91; MS (m/z): 1390.56$(M+1)^+$; TLC Rf: 0.30 (dichloromethane/methanol = 95/5); HPLC RT: 15.32 min (C8 reverse phase column: 250 mm; acetonitrile/water(0.05% TFA); operation temperature: 64 °C; Detector: 210 nm)].

Example 211

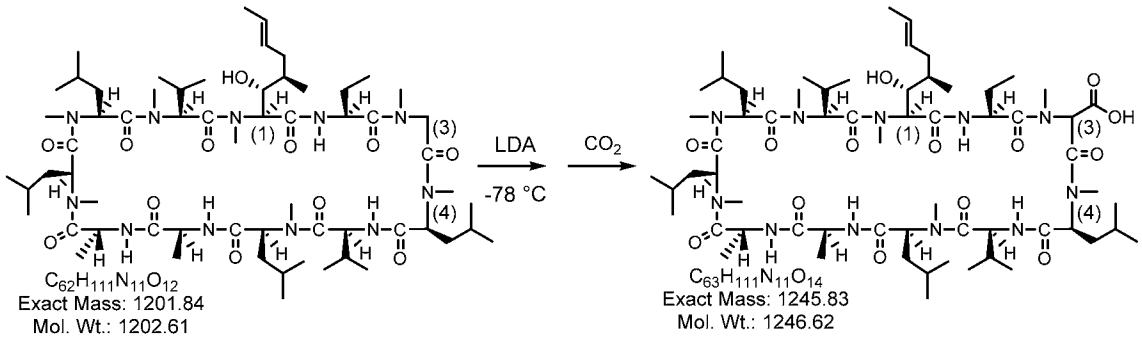
[(R)-3-Hydroxy-2-(hydroxylmethyl)propyl)-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin



[0353] To a suspension [(R)-3-ethoxy-2-(ethoxycarbonyl)-3-oxopropyl)-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (150 mg, 0.11 mmol) and lithium chloride (580 mg, 13.81 mmol) in methanol (50 ml) was added sodium borohydride (1.20 g, 31.75 mmol) in portions. The mixture was stirred overnight at room temperature. Most of solvent was evaporated under reduced pressure. Dichloromethane (100 ml) and water (50 ml) were added and separated. The dichloromethane layer was washed with brine, dried over Magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography (dichloromethane/methanol = 97/3) to give product. [Molecular formula: $C_{66}H_{119}N_{11}O_{15}$; Exact Mass: 1305.89; MS (m/z): 1306.48$(M+1)^+$; TLC Rf: 0.22 (dichloromethane/methanol = 9/1); HPLC RT: 10.65 min (C8 reverse phase column: 250 mm; acetonitrile/water(0.05% TFA); operation temperature: 64 °C; Detector: 210 nm)].

Reference Example 1

[α-Carboxy-Sar]-3-cyclosporin



[0354] n-Butyllithium (2.87 M, 27 mmol, 9.4 ml, 10 eq) was added to a solution of diisopropylamine (3.8 ml, 27 mmol, 10 eq) in tetrahydrofuran (80 ml) at –78 °C under nitrogen. After the reaction mixture was stirred for an hour, a solution of cyclosporine A (3.2 g, 2.66 mmol) in tetrahydrofuran (15 ml) was added over 10 min. The stirring was continued at –78 °C for 2 hours. Carbon dioxide gas was bubbled through the reaction mixture for 20-25 minutes and stirred at –78 °C for another hour. Then the cooling bath was removed and the reaction mixture was allowed to warm up to 0°C slowly. Most of

tetrahydrofuran was removed under vacuum at room temperature. The residue was quenched by the addition of saturated citric acid solution and the pH of the mixture was adjusted to around 7-8. The unreacted cyclosporin was extracted with ether (40 ml × 2). The PH of the aqueous layer was adjusted to 3~4 with 1 N hydrochloric acid and the precipitated oil was extracted with ethyl acetate (100 ml). The aqueous layer was extracted with ethyl acetate (100 ml × 3). The combined ethyl acetate layers were washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give semi-solid product (2.61 g, yield: 78%) [Molecular Formula: $C_{63}H_{111}N_{11}O_{14}$; Exact Mass: 1245.83; MS (m/z): 1246.7 $(M+1)^+$, 1268.7 $(M+Na)^+$].

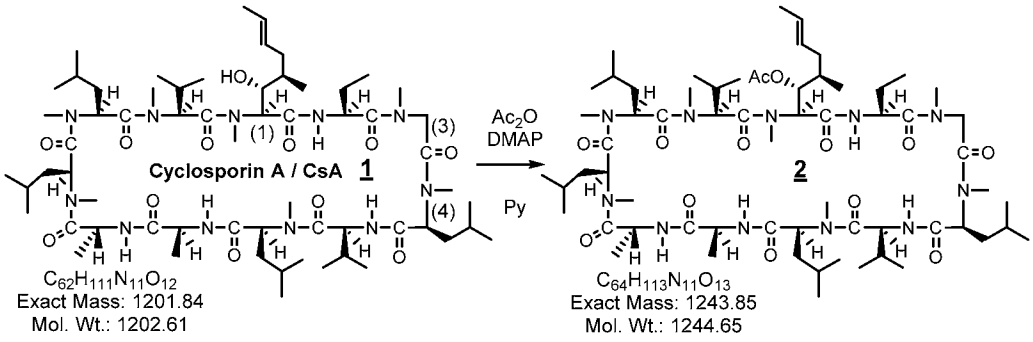
[0355] [α-Carboxy-Sar]-3-cyclosporin was synthesized according to a procedure described by Seebach D, et al., 1993, *Helv Chim Acta,* 76, 1564-1590.

Reference Example 2

Synthesis of [N-MeVal]-4-cyclosporin (SDZ-220-384)

[0356] [N-MeVal]-4-Cyclosporin (SDZ 220-384) was prepared according to procedures described by Papageorgiou C, et al., 1994, *Bioorg & Med Chem Lett*, **4**, 267-272 and its key cylosporine ring-opening between position 3 and 4 cited as reference 14: Su Z and Wenger R, Unpublished results; Papageorgiou C, et al., 1994, *J. Med. Chem.*, **37**, 3674-3676 and its key cylosporine ring-opening between position 3 and 4 cited as reference 11: Su Z and Wenger R, Unpublished results.

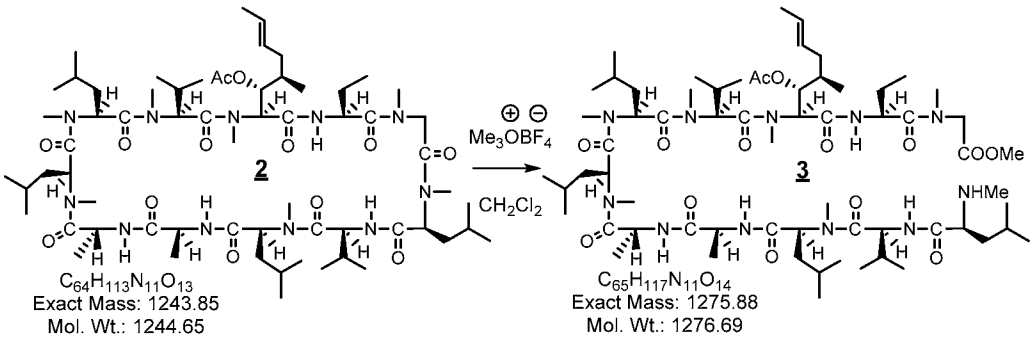
Cyclosporin A-acetate



[0357] To a solution of cyclosporin A (**1**) (12.00 g, 19.98 mmol) in acetic anhydride (MW: 102.09, d 1.082, 40 ml) were added pyridine (MW: 79.01, d 0.978, 40 ml) and 4-N,N-dimethylaminopyridine (MW: 122.17, 0.40 g). This mixture was stirred for overnight at room temperature, and then the mixture was diluted with 600 ml of ethyl acetate. The mixture was washed with brine, saturated ammonium chloride solution and 15% of sodium bicarbonate solution. The organic phase was dried over sodium sulphate, filtered and

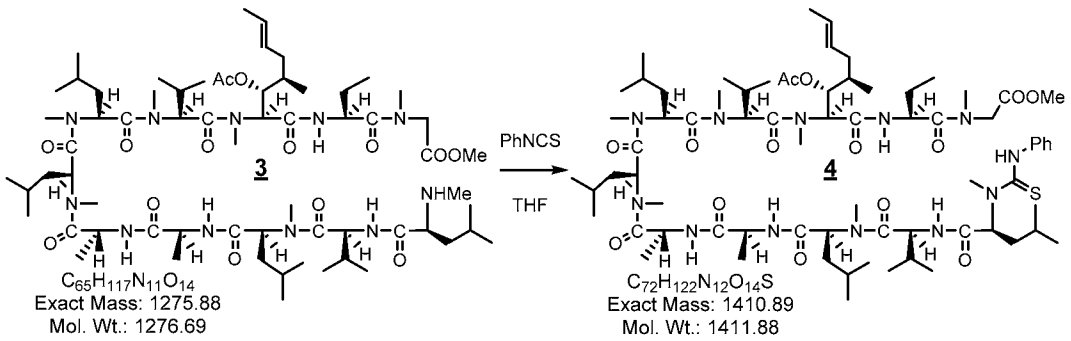
evaporated under the reduced pressure. Then all of pyridine was azeotropically evaporated out under the reduced pressure by adding toluene to the mixture to give a pale yellow solid residue, which was purified by flash chromatography on a silica gel column (100-200 mesh) with eluent of ethyl acetate/hexane (1/3) to give the 11.80 g (9.48 mmol, 95%) of cyclosporin A-acetate (**2**).

MeLeuValMeLeuAlaDAlaMeLeuMeLeuMeValMeBmt(OAc)AbuSar-Ome



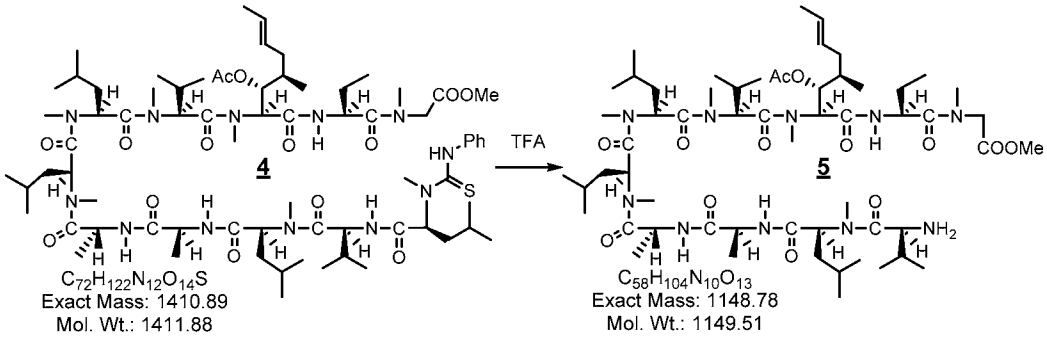
[0358] To a suspension of trimethyloxonium-fluoroborate (MW: 147.91, 2.96 g, 20 mmol, 2.50 equiv.) in dichloromethane (80 ml) was added cyclosporine A-acetate (**2**) (10.00 g, 8.00 mmol). The suspension was stirred for 18 hours at room temperature, and then a solution of sodium methoxide (9.90 mmol) in methanol (40 ml) was added. After the mixture was stirred for another half hour, 2 N solution of sulfuric acid in methanol (40 ml) was added. The mixture was stirred for 15-30 minutes at room temperature and neutralized with 15% potassium bicarbonate solution. Then the mixture was extracted twice with 700 ml of ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography on a silica column (100-200 mesh) with eluent of methanol/methyl t-butyl ether to give the 7.15 g (5.60 mmol, 70%) of linear undecapeptide peptide (**3**).

Phenylthiourea-MeLeuValMeLeuAlaDAlaMeLeuMeLeuMeValMeBmt(OAc)AbuSar-Ome



[0359] To a solution of linear undecapeptide peptide (**3**) (7.00 g, 5.50 mmol) in tetrahydrofuran (80 ml) was added phenyl isothiocyanate (MW: 135.19, d 1.130, 0.86 ml, 7.15 mmol, 1.30 equiv.). The mixture was stirred for 3 hours at room temperature and evaporated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (100-200 mesh) with eluent of acetone in hexane (1/5) to give the 6.99 g (4.95 mmol, 90%) of linear phenylthiourea undecapeptide (**4**) [Exact Mass: 1410.89; MS m/z: 1433.88 $(M+Na)^+$].

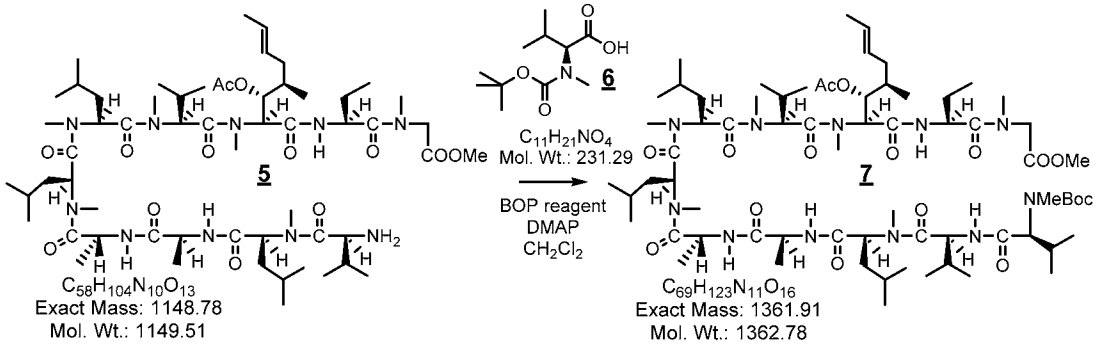
ValMeLeuAlaDAlaMeLeuMeLeuMeValMeBmt(OAc)AbuSar-Ome



[0360] To a solution of linear phenylthiourea undecapeptide (**4**) (6.80 g, 4.82 mmol) in toluene (300 ml) was added trifluoroacetic acid (MW: 114.02, d 1.480, 8.00 ml) at room temperature. The mixture was stirred for 1.5 to 2 hours and quenched by a slurry of sodium bicarbonate in water. Then the mixture was separated and the water phase was extracted with toluene (100 ml) and ethyl acetate (100 ml) subsequently. The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography on a silica column (100-200 mesh) with eluent of acetone/hexane (3/1) to give the 3.88 g (3.37 mmol, 70%) of linear decapeptide peptide (**5**) [Exact Mass: 1148.78; MS m/z: 1149.78 $(M+1)^+$].

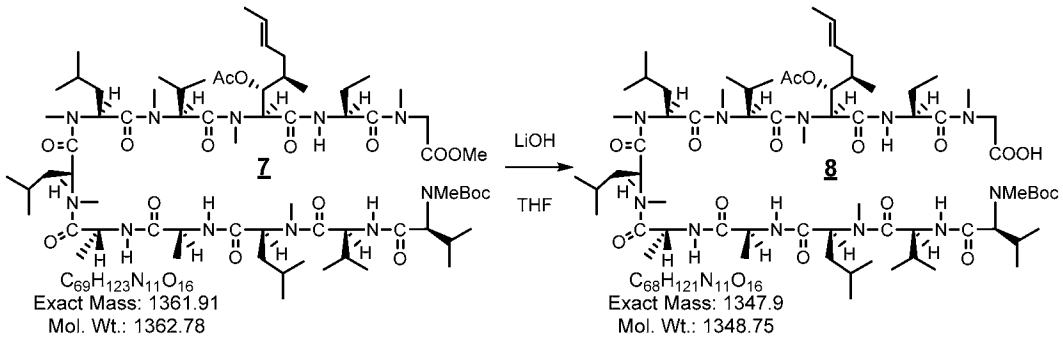
[0361] This Edman degradation was carried according to the similar method described by Edman P, et al, 1967, *Eur. J. Biochem.*, **1**, 80.

BocMeValValMeLeuAlaDAlaMeLeuMeLeuMeValMeBmt(OAc)AbuSar-Ome



[0362] To a solution of linear decapeptide peptide (**5**) (3.80 g, 3.30 mmol) in dichloromethane (150 ml) were added Boc-MeVal (**6**) (MW: 231.29, 0.92 g, 3.96 mmol, 1.2 equiv.), 1-propanephosphonic acid cyclic anhydride (MW: 318.18, 2.10 ml, 50 wt.% solution in ethyl acetate) and triethylamine (MW: 101.19, d 0.726, 0.46 ml, 3.30 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 5 hours. Then the mixture was washed with brine. The aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were dried over sodium sulphate. Removal of the solvent under reduced pressure gave the residue, which was purified by flash chromatography on a silica column (100-200 mesh) with eluent of acetone/hexane (1/2.5) to give the 4.05 g (2.97 mmol, 90%) of linear Boc-N-MeVal-decapeptide peptide (**7**) [Exact Mass: 1361.91; MS m/z: 1384.91 $(M+Na)^+$].

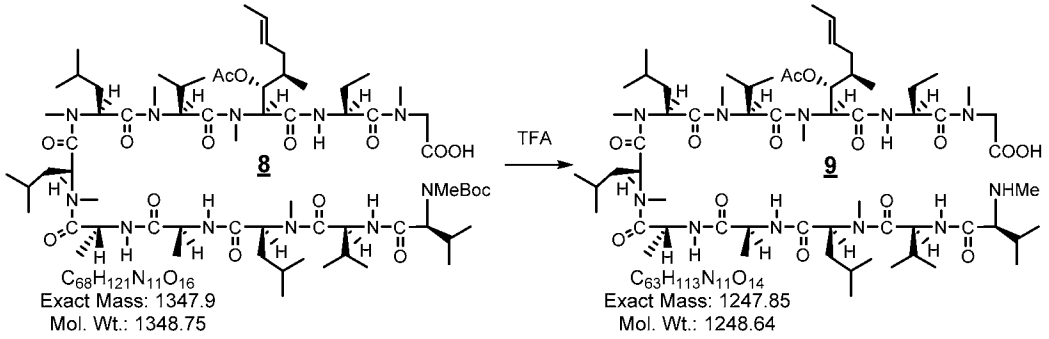
BocMeValValMeLeuAlaDAlaMeLeuMeLeuMeValMeBmt(OAc)AbuSar-OH



[0363] To a solution of linear [Boc-N-MeVal]-4-decapeptide peptide (**7**) (4.00 g, 2.94 mmol) in ethyl alcohol (150 ml) at 0 °C was added 0.5 N sodium hydroxide solution (7.1 ml, 1.20 equiv.). The mixture was stirred and kept at 0 °C for 16 hours. Then the PH of the mixture was adjusted to around 3 by adding 0.5 N hydrochloric acid. Most of solvent was evaporated under the reduced pressure and the residue was dissolved in 200ml of ethyl acetate. The mixture was washed with a pH 3 buffer, dried over sodium sulphate, filtered and evaporated under the reduced pressure. The residue was purified by flash

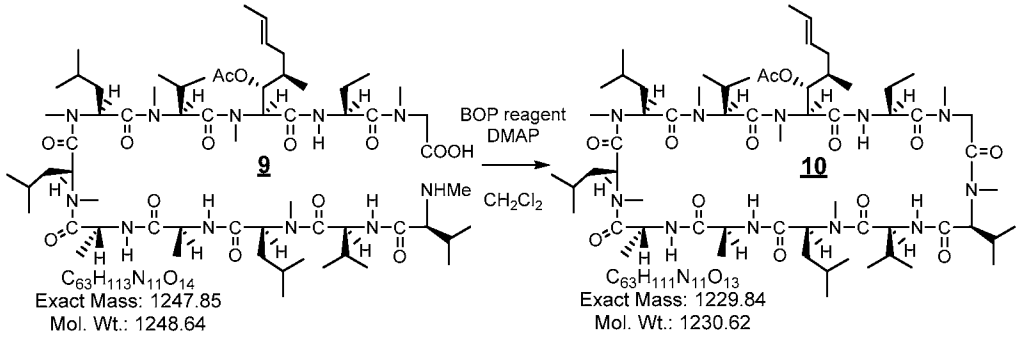
chromatography on a silica column (100-200 mesh) with eluent of methanol/ethyl acetate (1/8) to yield 2.55 g (1.89 mmol, 64.3%) of the free acid (**8**).

MeValValMeLeuAlaDAlaMeLeuMeLeuMeValMeBmt(OAc)AbuSar-OH



[0364] To a solution of free acid (**8**) (2.55g, 1.89 mmol) in dichloromethane (25 ml) was slowly added 5 ml of trifluoroacetic acid (MW: 114.02, d 1.480) at 0 °C. The solution was stirred at room for 2 hours. Then ethyl acetate (300 ml) was added and the solvent was removed under reduced pressure. Another ethyl acetate (300 ml) was added and the solvent was removed under reduced pressure again. The residue was purified by flash chromatography on a silica gel column (100-200 mesh) with eluent of methanol/acetone (1/3) to give the 2.01g (1.61 mmol, 85%) of linear [N-MeVal]-4-decapeptide peptide free acid (**9**) [Exact Mass: 1247.85; MS m/z: 1248.85 $(M+1)^+$].

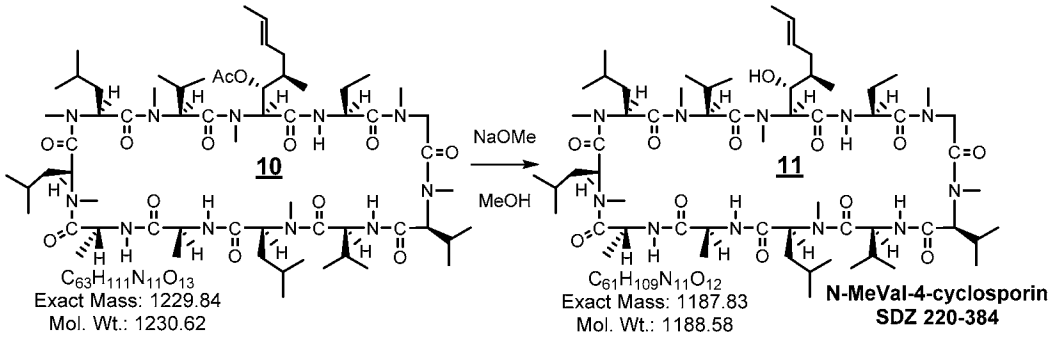
[N-MeVal]-4-Cyclosporin acetate



[0365] To a solution of linear [N-MeVal]-4-decapeptide peptide free acid (**9**) (1.03 g, 0.83 mmol) in dichloromethane (250 ml) were added 1-propanephosphonic acid cyclic anhydride (MW: 318.18, 0.53 ml, 50wt.% solution in ethyl acetate), 2,4,6-collidine (MW: 121.18, d 0.917, 0.11 ml, 0.83 mmol)) at 0 °C. The mixture was stirred at room temperature for 24 hours. Then the mixture was passed through a thin layer of silica gel and washed twice by 40 ml of ethyl acetate. The collected organic solution was evaporated under the reduced pressure. The residue was purified by flash chromatography on a silica gel column (230-400 mesh) with eluent of methanol/acetone (1/6) to give the 611 mg (0.50 mmol,

60%) of (N-Methyl-Val)-4-Cyclosporin acetate (**10**) [Exact Mass: 1229.84; MS m/z: 1252.82 $(M+Na)^+$].

[N-MeVal]-4-Cyclosporin



[0366] To a solution of [N-MeVal]-4-Cyclosporin acetate (**10**) (0.60 g, 0.49 mmol) in methanol (40 ml) was added a solution of sodium methoxide in methanol (0.5 M, 1.9 ml, 2.0 equiv.). The mixture was stirred for 0.5 hour at 0 °C and 24 hours at room temperature. The PH of the mixture was adjusted to around 6 by adding 0.5 N hydrochloric acid. After the solvent was evaporated under reduced pressure, the residue was dissolved in 200 ml of ethyl acetate. The organic solution was washed by aqueous sodium bicarbonate and brine, dried over sodium sulphate and filtered. After removal of solvent, the residue was purified by flash chromatography on a silica gel column (230-400 mesh) with eluent of acetone/hexane (1/2) to give the 406 mg (0.34 mmol, 70%) of [N-MeVal]-4-Cyclosporin (**11**) [Exact Mass: 1187.83;84; MS m/z: 1210.81 (M+Na].

Reference Example 3

[0367] [N-MeIle]-4-Cyclosporin (NIM-811) was prepared according to the procedure used for the synthesis of (N-MeVal)-4-cyclosporin (SDZ 220-384).

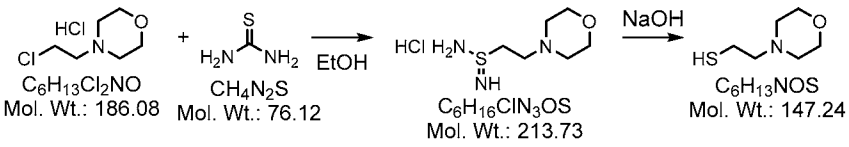
Reference Example 4

[0368] [N-MeThr]-4-Cyclosporin can be prepared according to the procedure used for the synthesis of (N-MeVal)-4-cyclosporin (SDZ 220-384).

Reference Example 5

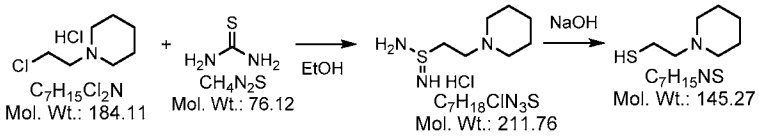
[0369] The side chain intermediates were synthesized according to procedures described by Urquhart GG, 1994, *Org Synth, Coll. Vol III,* 363.

2-Morpholinoethanethiol



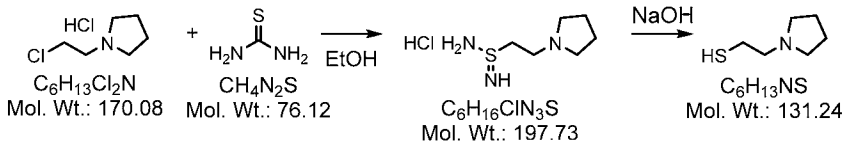
[0370] A mixture of 4-(2-chloroethyl)morpholine (7.00 g, 37 mmol) and thiourea (2.90 g, 38 mmol) in 95% ethanol (55 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (3.40 g, 85 mmol) in water (20 ml) was added, and the mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with benzene. The benzene layer was washed with brine, dried over magnesium sulfate and evaporated to provide 3.80 g of crude product, which was used for the addition reaction.

2-(N-Piperidinyl)ethanethiol



[0371] The mixture of 1-(2-chloroethyl)piperidine hydrochloride (7.00 g, 38 mmol) and thiourea (4.60 g, 61 mmol) in 95% ethanol (30 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (2.40 g) in water (20 ml) was added. The mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with ether. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3.20 g of crude product, which was used for the addition reaction without purification.

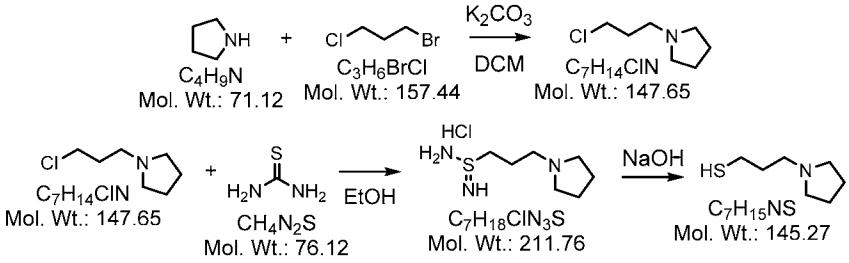
2-(N-Pyrrolidinyl)ethanethiol



[0372] The mixture of 1-(2-chloroethyl)piperidine hydrochloride (7.0 g, 41 mmol) and thiourea (3.20 g, 40 mmol) in 95% ethanol (30 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (3.40 g, 85 mmol) in water (20 ml) was added. The mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with benzene. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced

pressure to give 3.80 g of crude product, which was used for the addition reaction without purification.

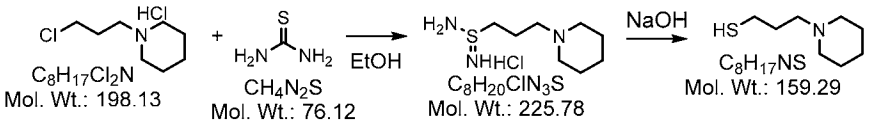
3-(N-Pyrrolidinyl)propanethiol



[0373] To a suspension of 1-bromoro-3-chloropropane (30.00 g, 191 mmol) and potassium carbonate (17.00 g, 123 mmol) in dichloromethane (160 ml) was added pyrrolidine (3.50 g, 49 mmol) portions. The mixture was stirred at room temperature overnight. Then the mixture was filtered and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate/methanol = 95/5) to give 6.00 g of product.

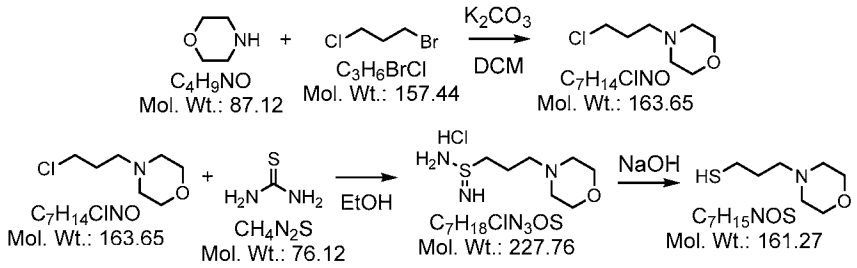
[0374] A mixture of 1-(3-chloropropyl)pyrrolidine (3.4 g, 23 mmol) and thiourea (1.8 g, 23 mmol) in 95% ethanol (55 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (1.20 g, 30 mmol) in water (10 ml) was added, and the mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with benzene. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 1.80 g of crude product, which was used for the addition reaction.

3-(N-Piperidinyl)propanethiol



[0375] The mixture of 1-(3-chloropropyl)piperidine hydrochloride (7.50 g, 38 mmol) and thiourea (4.60 g, 61 mmol) in 95% ethanol (30 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (2.40 g) in water (20 ml) was added. The mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with ether. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3.50 g of crude product, which was used for the addition reaction without purification.

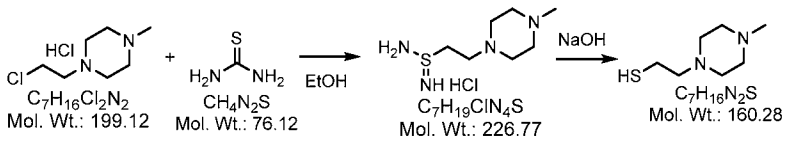
3-Morpholinopropanethiol



[0376] To a suspension of 1-bromoro-3-chloropropane (30.00 g, 191 mmol) and potassium carbonate (14.00 g, 101 mmol) in dichloromethane (160 ml) was added morpholine (4.00 g, 46 mmol) in portions. Then the mixture was stirred at room temperature overnight. The mixture was filtered and evaporated under reduced pressure. The residue was purified by chromatography (ethyl acetate) to give 5.60 g of product.

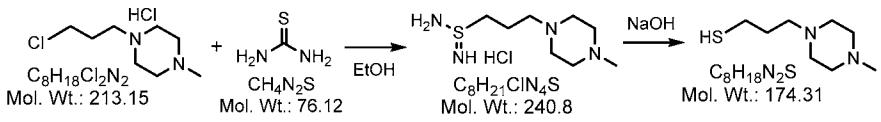
[0377] A mixture of 1-(3-chloropropyl)morpholine (4.20 g, 25.76 mmol) and thiourea (2.00 g, 26.27 mmol) in 95% ethanol (55 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (1.3 g, 32.50 mmol) in water (10 ml) was added, and the mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with benzene. The benzene layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 2.20 g of crude product, which was used for the addition reaction.

2-(4-Methyl-N-piperazinyl)ethanethiol



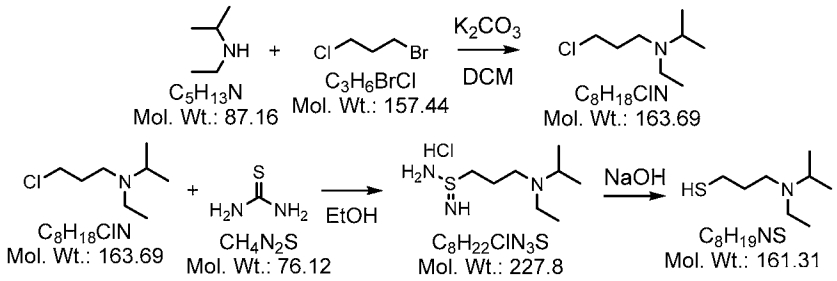
[0378] A mixture of 2-(4-methylpiperazino)ethyl chloride (8.00 g, 40 mmol) and thiourea (4.87 g, 64 mmol) in 95% ethanol (55 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (2.60 g) in water (20 ml) was added, and the mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with benzene. The benzene layer was washed with brine, dried magnesium sulfate and evaporated to provide 3.0 g of crude product, which was used for the addition reaction.

3-(4-Methyl-N-piperazinyl)propanethiol



[0379] A mixture of 3-(4-methylpiperazino)propyl chloride (8.5 g, 40 mmol) and thiourea (4.87 g, 64 mmol) in 95% ethanol (70 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (2.6 g) in water (20 ml) was added, and the mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with ether. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to provide 2.5 g of crude product, which was used for the addition reaction.

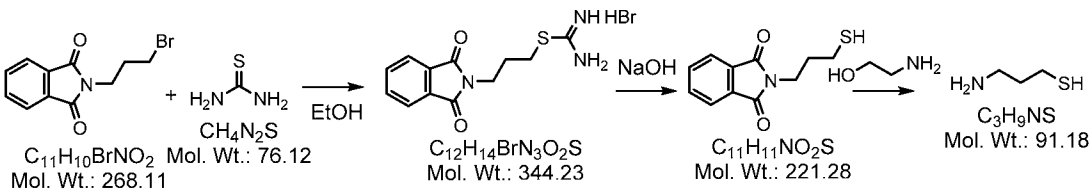
3-(N-Ethyl-N-isopropylamino)propanethiol



[0380] To a suspension of 1-bromoro-3-chloropropane (11.00 g, 70 mmol) and potassium carbonate (13.00 g, 94 mmol) in dichloromethane (100 ml) was added ethylisopropylamine (4.10 g, 47 mmol) in portions. The mixture was stirred at room temperature overnight. The mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography (ethyl acetate/methanol = 95/5) to give 6.10 g of product.

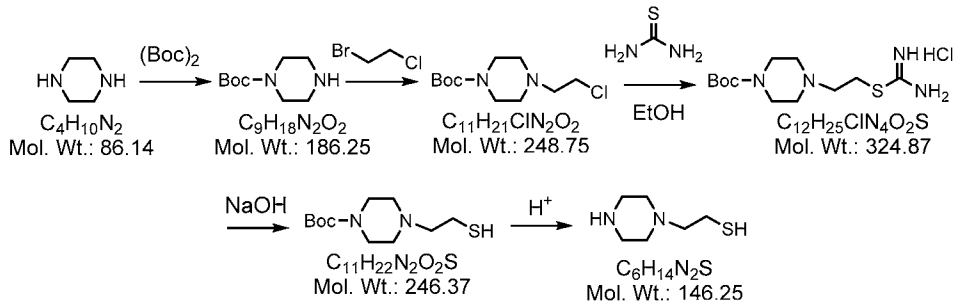
[0381] A mixture of 3-chloropropylethylisopropylamiune (4.20 g, 25.66 mmol) and thiourea (2.00 g, 26.32 mmol) in 95% ethanol (55 ml) was heated to reflux for 24 hours. A solution of sodium hydroxide (1.30 g, 32.50 mmol) in water (10 ml) was added, and the mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with benzene. The benzene layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 1.20 g of crude product, which was used for the addition reaction.

3-Aminopropanethiol



[0382] A mixture of N-(3-bromopropyl)phthalimide (20.00 g, 74.63 mmol) and thiourea (9.98 g, 131.34 mmol) in 95% ethanol (80 ml) was heated to reflux for 3 hours. A solution of sodium hydroxide (4.48 g, 111.94 mmol) in water (30 ml) was added, and the mixture was continued to reflux for another 3 hours. After cooled to room temperature, the mixture was evaporated under reduced pressure. The residue was mixed with ethyl acetate (50 ml) and brine (50 ml). The organic layer was separated and washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was mixed with toluene (100 ml) and heated to reflux with removal of water azeotropically for two hours. After removal of toluene, the residue was purified by chromatography on silica gel with hexane and ethyl acetate as solvent to give 9.10 g of N-(3-mercaptopropyl)phthalimide. To a solution of N-(3-mercaptopropyl)phthalimide in methanol (50 ml) was added ethanolamine. The mixture was stirred and heated to reflux for two hours. After cooled to room temperature, the mixture was used for the addition reaction without further purification.

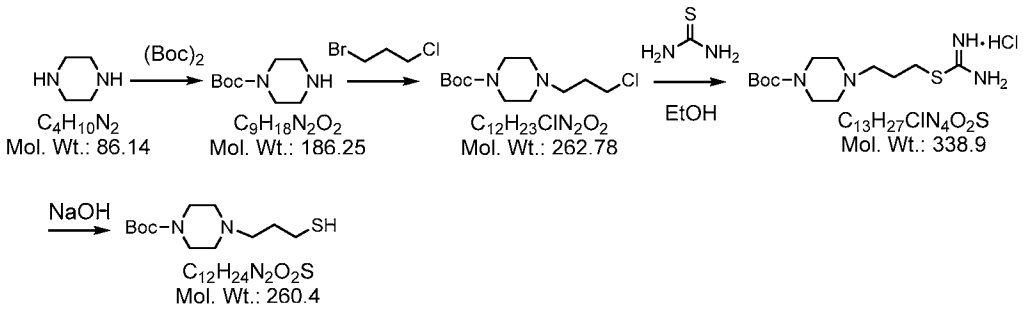
2-Mercaptoethylpiperazine



[0383] To a suspension of piperizaine (30.00 g, 348.27 mmol) and sodium carbonate (106 g, 348.27 mmol) in dichloromethane (200 ml) was added dropwise a solution of Di-tert-butyl dicarbonate (18.98 g, 87.07 mmol) in dichloromethane (30 ml) at room temperature for one hour. Then the mixture was stirred at room temperature overnight. The mixture was mixed with water (100 ml) and separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in dichloromethane (150 ml). Sodium carbonate (15.55 g, 146.77 mmol) and 1-bromo-2-chloroethane (21.05 g, 146.77 mmol) were added. The mixture was stirred at room temperature for a weekend. The mixture was mixed with water (100 ml) and separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using hexane and ethyl acetate as eluent to give 6.85 g of 1-Boc-4-(2-chloroethyl)piperazine.

[0384] To a solution of 1-Boc-4-(2-chloroethyl)piperazine (6.85 g, 27.62 mmol) in methanol (50 ml) was added thiourea (4.12 g, 55.24 mmol). The mixture was heated to reflux for 2 hours. A solution of sodium hydroxide (1.66 g, 41.43 mmol) in water (10 ml) was added, and the mixture was continued to reflux for another hour. Then most solvent was evaporated under reduced pressure. The residue was mixed with ethyl acetate (50 ml) and brine (30 ml) and separated. The ethyl acetate was dried over magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in methanol (20 ml). 4 M hydrochloric acid in dioxane (10 ml) was added. The mixture was stirred at room temperature overnight and most of solvent was evaporated under reduced pressure. The residue was used for the addition reaction without further purification.

1-Boc-4-(3-mercaptopropanyl)piperazine



[0385] To a suspension of piperizaine (30.00 g, 348.27 mmol) and sodium carbonate (106 g, 348.27 mmol) in dichloromethane (200 ml) was added dropwise a solution of Di-tert-butyl dicarbonate (18.98 g, 87.07 mmol) in dichloromethane (30 ml) at room temperature for one hour. Then the mixture was stirred at room temperature overnight. The mixture was mixed with water (100 ml) and separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in dichloromethane (100 ml). Sodium carbonate (15.44 g, 145.70 mmol) and 1-bromo-3-chloropropane (15.29 g, 97.13 mmol) were added. The mixture was stirred at room temperature overnight. The mixture was mixed with water (80 ml) and separated. The dichloromethane layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using hexane and ethyl acetate as eluent to give 11.77 g of 1-Boc-4-(3-chloropropanyl)piperazine.

[0386] To a solution of 1-Boc-4-(3-chloropropanyl)piperazine (11.77 g, 44.90 mmol) in ethanol (100 ml) was added thiourea (6.82 g, 89.80 mmol). The mixture was heated to reflux for 4 hours. A solution of sodium hydroxide (2.69 g, 67.35 mmol) in water (40 ml) was added, and the mixture was continued to reflux for another 2 hours. Then most solvent

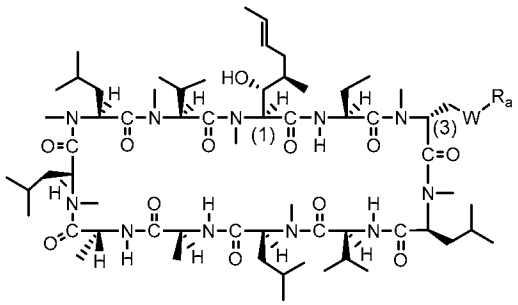
was evaporated under reduced pressure. The residue was mixed with ethyl acetate (100 ml) and brine (50 ml) and separated. The ethyl acetate was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel using hexane and acetone as eluent to give 7.5 g of tert-butyl 4-N-Boc-1-(3-mercaptopropanyl)piperazine.

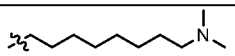
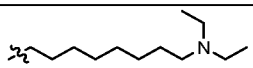
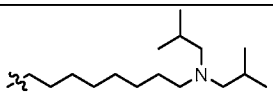
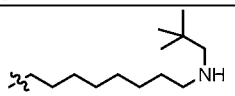
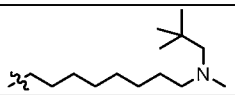
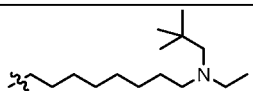
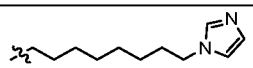
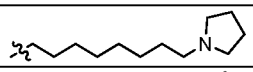
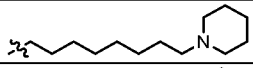
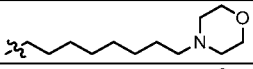
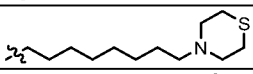
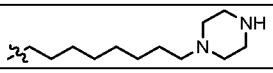
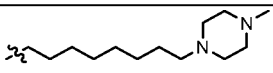
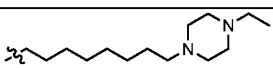
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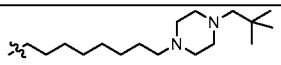
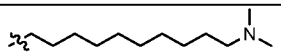
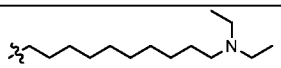
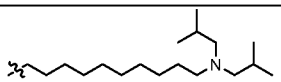
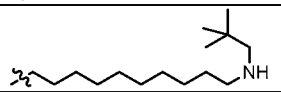
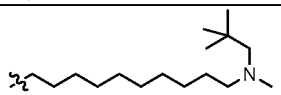
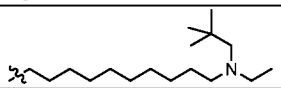
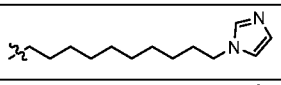
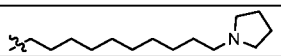
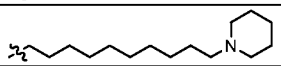
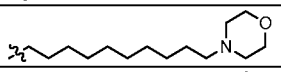
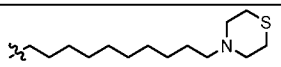
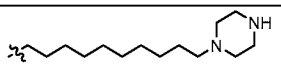
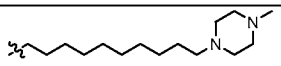
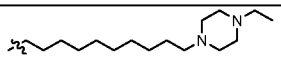
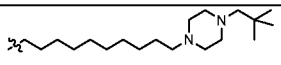
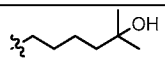
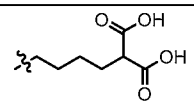
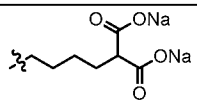
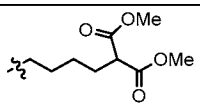
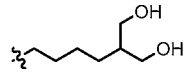
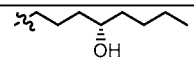
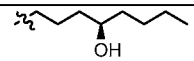
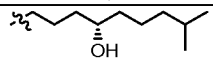
Cyclosporin Derivatives

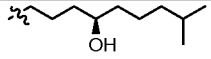
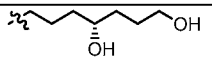
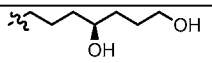
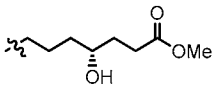
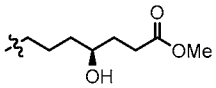
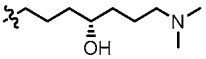
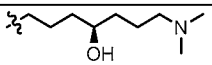
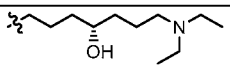
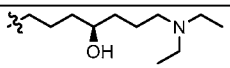
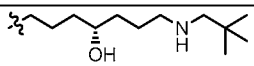
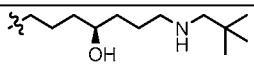
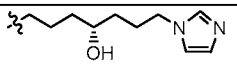
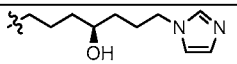
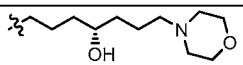
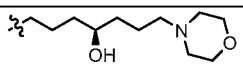
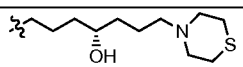
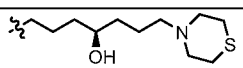
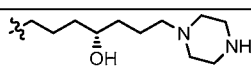
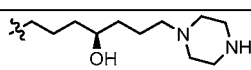
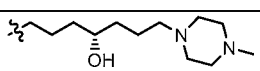
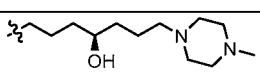
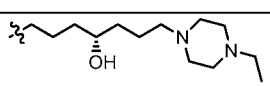
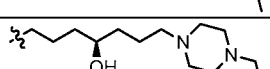
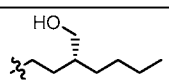
[0387] The following compounds can be prepared according to a method analogous to those described herein.

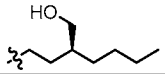
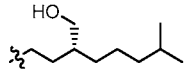
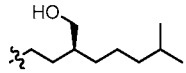
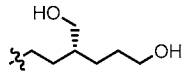
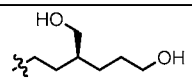
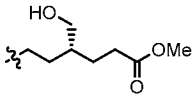
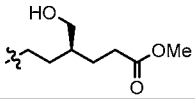
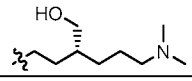
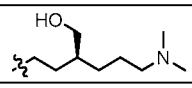
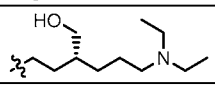
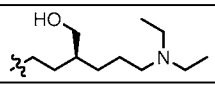
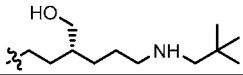
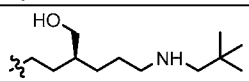
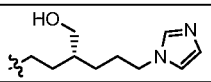
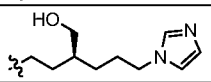
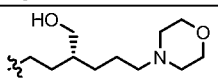
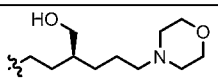
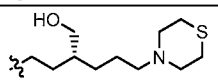
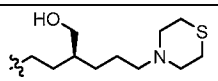
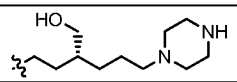
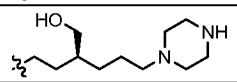
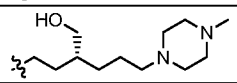
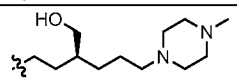
Table 1

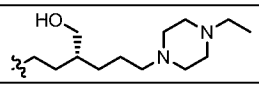
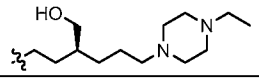
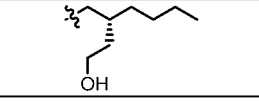
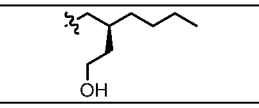
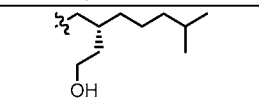
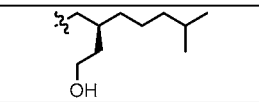
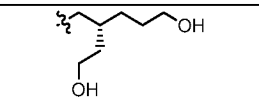
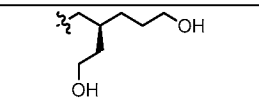
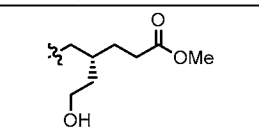
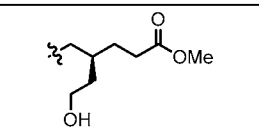
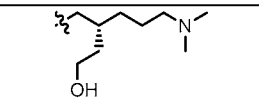
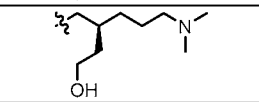
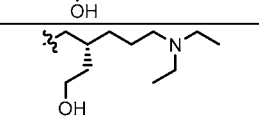
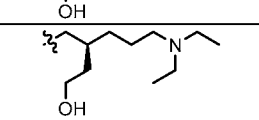
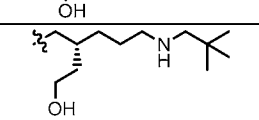
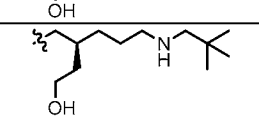
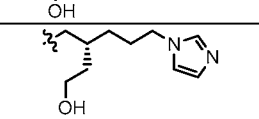
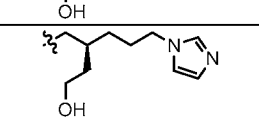


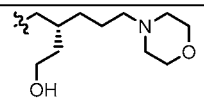
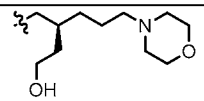
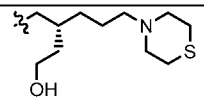
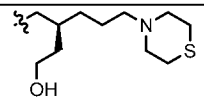
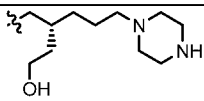
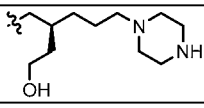
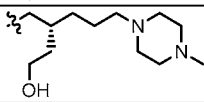
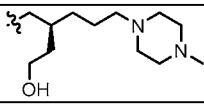
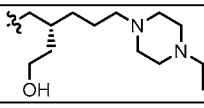
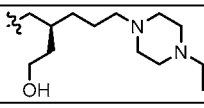
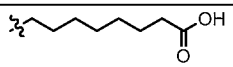
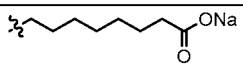
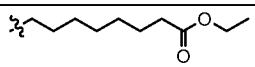
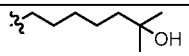
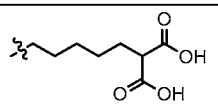
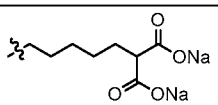
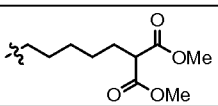
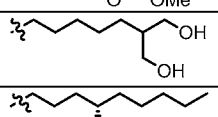
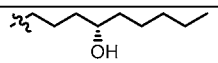
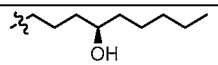
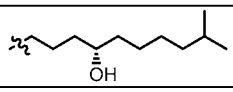
Ex. No.	W	R_a	Name
212	S		[(S)-(8-(N,N-Dimethylamino)octylthio)methyl-Sar]-3-cyclosporin
213	S		[(S)-(8-(N,N-Diethylamino)octylthio)methyl-Sar]-3-cyclosporin
214	S		[(S)-(8-(N,N-Diisobutylamino)octylthio)methyl-Sar]-3-cyclosporin
215	S		[(S)-(8-(Neopentylamino)octylthio)methyl-Sar]-3-cyclosporin
216	S		[(S)-(8-(Methyl(neopentyl)amino)octylthio)methyl-Sar]-3-cyclosporin
217	S		[(S)-(8-(Ethyl(neopentyl)amino)octylthio)methyl-Sar]-3-cyclosporin
218	S		[(S)-(8-(1H-Imidazol-1-yl)octylthio)methyl-Sar]-3-cyclosporin
219	S		[(S)-(8-(Pyrrolidin-1-yl)octylthio)methyl-Sar]-3-cyclosporin
220	S		[(S)-(8-(Piperidin-1-yl)octylthio)methyl-Sar]-3-cyclosporin
221	S		[(S)-((8-Morpholinooctyl)thio)methyl-Sar]-3-cyclosporin
222	S		[(S)-((8-Thiomorpholinooctyl)thio)methyl-Sar]-3-cyclosporin
223	S		[(S)-((8-(Piperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
224	S		[(S)-((8-(4-Methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
225	S		[(S)-((8-(4-Ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin

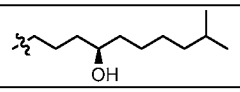
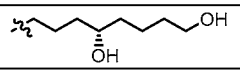
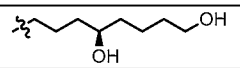
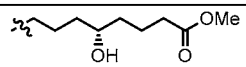
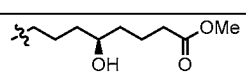
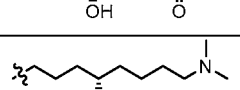
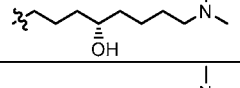
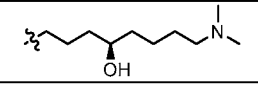
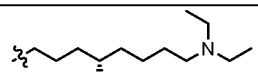
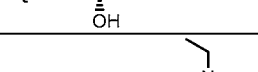
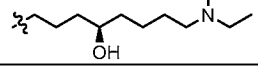
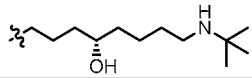
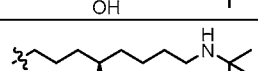
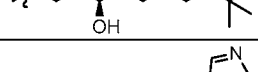
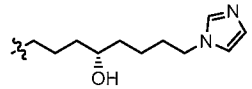
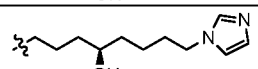
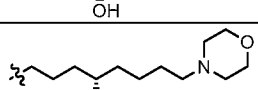
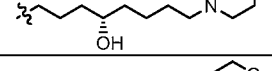
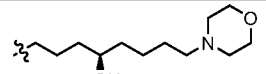
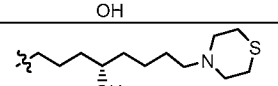
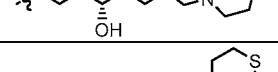
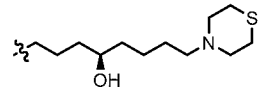
226	S		[(S)-((8-(4-Neopentylpiperazin-1-yl)octylthio)methyl-Sar]-3-cyclosporin
227	S		[(S)-(10-(N,N-Dimethylamino)decylthio)methyl-Sar]-3-cyclosporin
228	S		[(S)-(10-(N,N-Diethylamino)decylthio)methyl-Sar]-3-cyclosporin
229	S		[(S)-(10-(N,N-Diisobutylamino)decylthio)methyl-Sar]-3-cyclosporin
230	S		[(S)-(10-(Neopentylamino)decylthio)methyl-Sar]-3-cyclosporin
231	S		[(S)-(10-(methyl(neopentyl)amino)decylthio)methyl-Sar]-3-cyclosporin
232	S		[(S)-(10-(Ethyl(neopentyl)amino)decylthio)methyl-Sar]-3-cyclosporin
233	S		[(S)-(10-(1H-imidazol-1-yl)decylthio)methyl-Sar]-3-cyclosporin
234	S		[(S)-(10-(Pyrrolidin-1-yl)decylthio)methyl-Sar]-3-cyclosporin
235	S		[(S)-(10-(Piperidin-1-yl)decylthio)methyl-Sar]-3-cyclosporin
236	S		[(S)-((10-Morpholinodecyl)thio)methyl-Sar]-3-cyclosporin
237	S		[(S)-((10-Thiomorpholinodecyl)thio)methyl-Sar]-3-cyclosporin
238	S		[(S)-((10-(Piperazin-1-yl)decyl)thio)methyl-Sar]-3-cyclosporin
239	S		[(S)-((10-(4-Methylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-cyclosporin
240	S		[(S)-((10-(4-Ethylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-cyclosporin
241	S		[(S)-((10-(4-Neopentylpiperazin-1-yl)decylthio)methyl-Sar]-3-cyclosporin
242	S		[(S)-((5-Hydroxy-5-methylhexyl)thio)methyl-Sar]-3-cyclosporin
243	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-cyclosporin
244	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-cyclosporin-disodium salt
245	S		[(S)-((6-Methoxy-5-(methoxycarbonyl)-6-oxohexyl)thio)methyl-Sar]-3-cyclosporin
246	S		[(S)-((6-Hydroxy-5-hydroxymethylhexyl)thio)methyl-Sar]-3-cyclosporin
247	S		[(S)-((S)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-cyclosporin
248	S		[(S)-((R)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-cyclosporin
249	S		[(S)-((S)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-cyclosporin

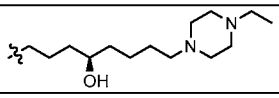
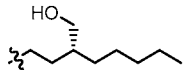
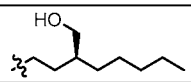
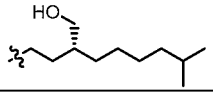
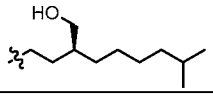
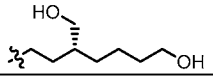
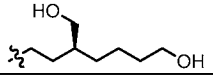
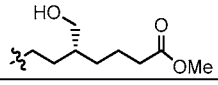
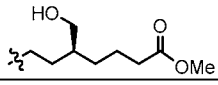
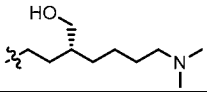
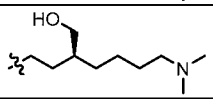
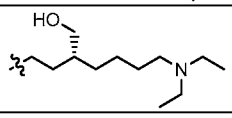
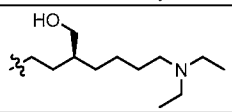
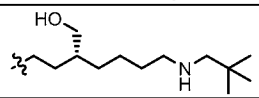
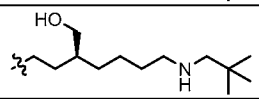
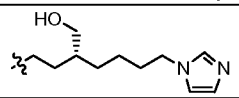
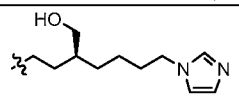
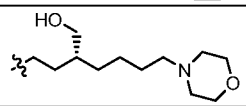
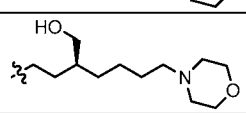
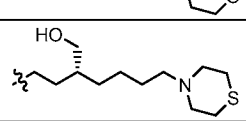
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251	S		[(S)-((S)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-cyclosporin
252	S		[(S)-((R)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-cyclosporin
253	S		[(S)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-cyclosporin
254	S		[(S)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-cyclosporin
255	S		[(S)-(((S)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
256	S		[(S)-(((R)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
257	S		[(S)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
258	S		[(S)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
259	S		[(S)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
260	S		[(S)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
261	S		[(S)-(((S)-4-Hydroxy-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-cyclosporin
262	S		[(S)-(((R)-4-Hydroxy-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-cyclosporin
263	S		[(S)-(((S)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
264	S		[(S)-(((R)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
265	S		[(S)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
266	S		[(S)-(((R)-4-Hydroxy-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
267	S		[(S)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-cyclosporin
268	S		[(S)-(((R)-4-Hydroxy-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-cyclosporin
269	S		[(S)-(((S)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
270	S		[(S)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
271	S		[(S)-(((S)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
272	S		[(S)-(((R)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
273	S		[(S)-(((R)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-cyclosporin

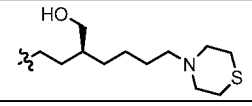
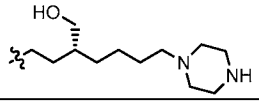
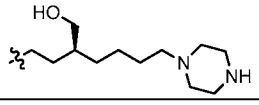
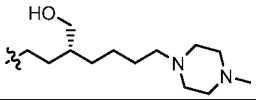
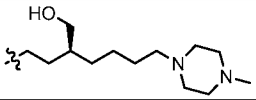
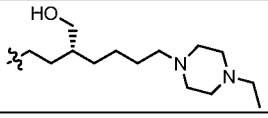
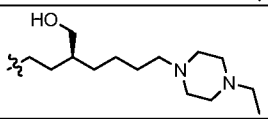
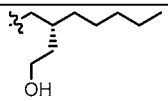
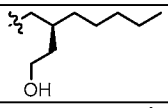
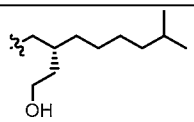
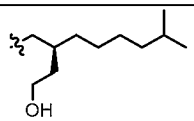
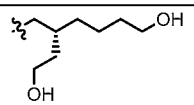
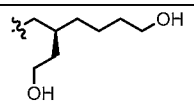
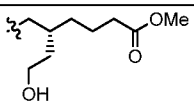
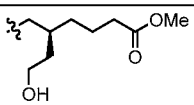
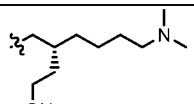
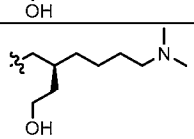
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275	S		[(S)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-cyclosporin
276	S		[(S)-(((S)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-cyclosporin
277	S		[(S)-(((R)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-cyclosporin
278	S		[(S)-(((S)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-cyclosporin
279	S		[(S)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-cyclosporin
280	S		[(S)-(((S)-3-Hydroxy-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-cyclosporin
281	S		[(S)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
282	S		[(S)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
283	S		[(S)-(((R)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
284	S		[(S)-(((S)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
285	S		[(S)-(((R)-3-Hydroxy-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
286	S		[(S)-(((S)-3-Hydroxy-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
287	S		[(S)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-cyclosporin
288	S		[(S)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-cyclosporin
289	S		[(S)-(((R)-3-Hydroxymethyl-6-morpholinohexyl)thio)methyl-Sar]-3-cyclosporin
290	S		[(S)-(((S)-3-Hydroxymethyl-6-morpholinohexyl)thio)methyl-Sar]-3-cyclosporin
291	S		[(S)-(((R)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-cyclosporin
292	S		[(S)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-cyclosporin
293	S		[(S)-(((R)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-cyclosporin
294	S		[(S)-(((S)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-cyclosporin
295	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-cyclosporin
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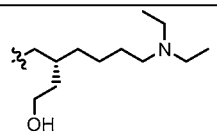
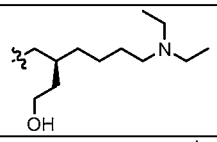
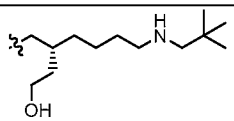
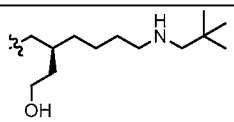
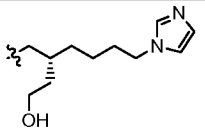
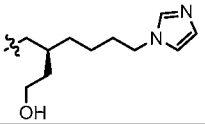
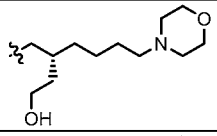
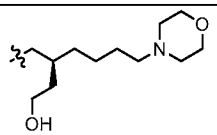
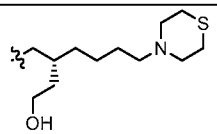
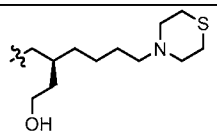
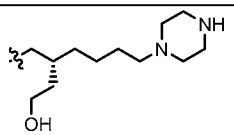
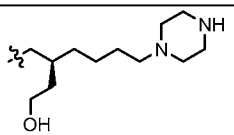
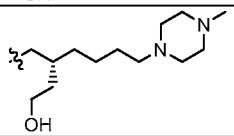
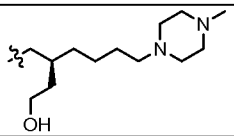
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299	S		[(S)-(((R)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-cyclosporin
300	S		[(S)-(((S)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-cyclosporin
301	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-cyclosporin
302	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-cyclosporin
303	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-cyclosporin
304	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-cyclosporin
305	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-cyclosporin
306	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-cyclosporin
307	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-cyclosporin
308	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-cyclosporin
309	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-cyclosporin
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311	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-cyclosporin
312	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-cyclosporin
313	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-cyclosporin
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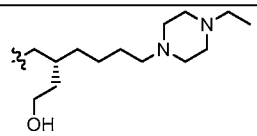
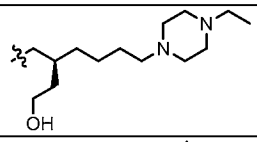
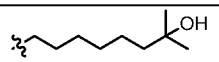
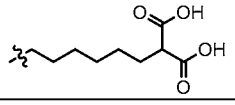
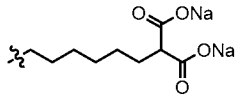
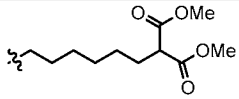
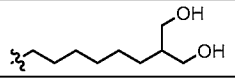
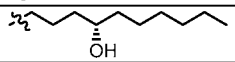
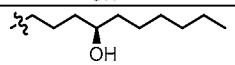
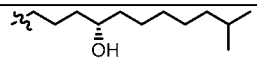
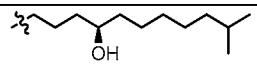
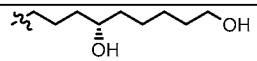
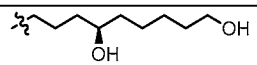
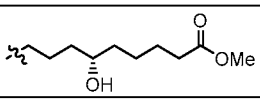
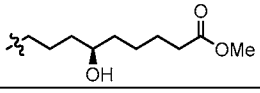
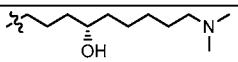
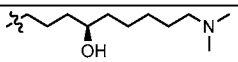
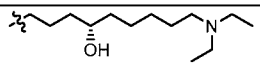
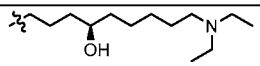
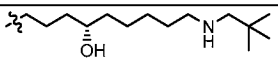
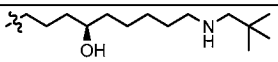
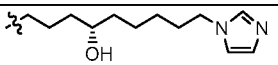
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316	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-cyclosporin
317	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-cyclosporin
318	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-cyclosporin
319	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-cyclosporin
320	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-cyclosporin
321	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-cyclosporin
322	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-cyclosporin
323	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-cyclosporin
324	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-cyclosporin
325	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-cyclosporin
326	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-cyclosporin-sodium salt
327	S		[(S)-(7-(Ethoxycarbonyl)heptylthio)methyl-Sar]-3-cyclosporin
328	S		[(S)-((6-Hydroxy-6-methylheptyl)thio)methyl-Sar]-3-cyclosporin
329	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-cyclosporin
330	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-cyclosporin-disodium salt
331	S		[(S)-((7-Methoxy-6-(methoxycarbonyl)-7-oxoheptyl)thio)methyl-Sar]-3-cyclosporin
332	S		[(S)-((7-Hydroxy-6-hydroxymethylheptyl)thio)methyl-Sar]-3-cyclosporin
333	S		[(S)-((S)-(4-Hydroxynonyl)thio)methyl-Sar]-3-cyclosporin
334	S		[(S)-((R)-(4-Hydroxynonyl)thio)methyl-Sar]-3-cyclosporin
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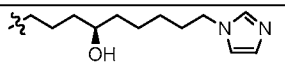
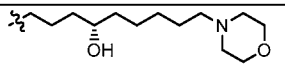
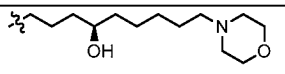
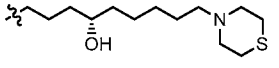
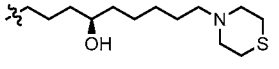
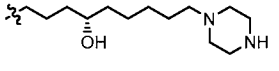
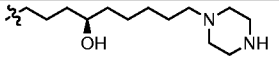
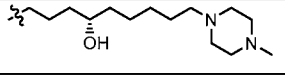
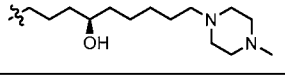
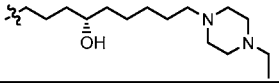
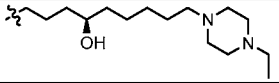
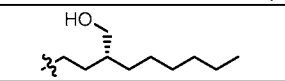
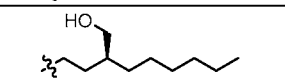
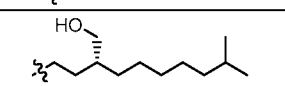
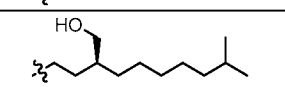
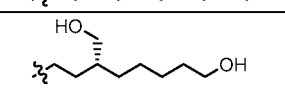
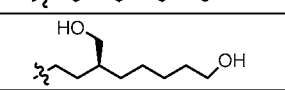
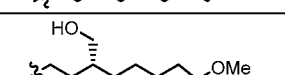
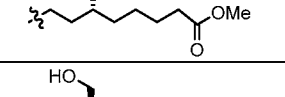
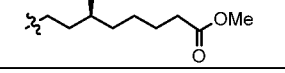
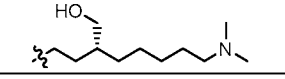
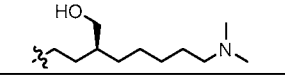
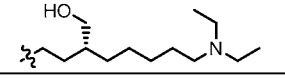
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339	S		[(S)-(((S)-4-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-cyclosporin
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341	S		[(S)-(((S)-4-Hydroxy-8-(dimethylamino)octyl)thio)methyl-Sar]-3-cyclosporin
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346	S		[(S)-(((R)-4-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-cyclosporin
347	S		[(S)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
348	S		[(S)-(((R)-4-Hydroxy-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
349	S		[(S)-(((S)-4-Hydroxy-8-morpholinooctyl)thio)methyl-Sar]-3-cyclosporin
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356	S		[(S)-(((R)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
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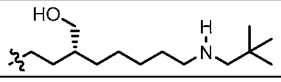
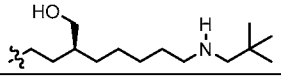
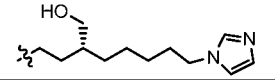
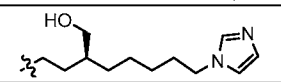
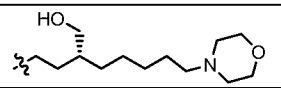
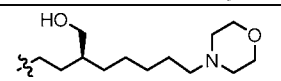
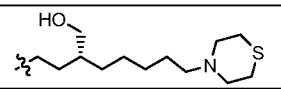
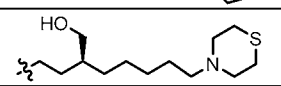
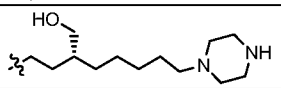
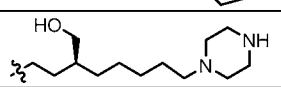
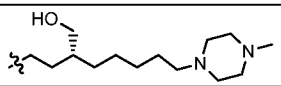
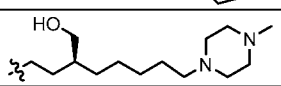
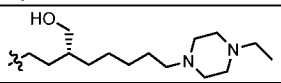
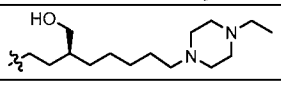
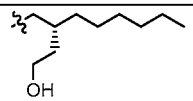
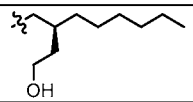
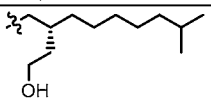
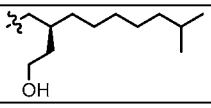
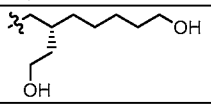
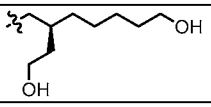
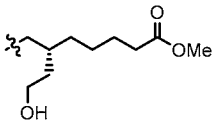
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360	S		[(S)-(((S)-3-(Hydroxymethyl)octyl)thio)methyl-Sar]-3-cyclosporin
361	S		[(S)-(((R)-3-(Hydroxymethyl)-8-methylnonyl)thio)methyl-Sar]-3-cyclosporin
362	S		[(S)-(((S)-3-(Hydroxymethyl)-8-methylnonyl)thio)methyl-Sar]-3-cyclosporin
363	S		[(S)-((((R)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)thio)methyl-Sar]-3-cyclosporin
364	S		[(S)-((((S)-3-(Hydroxymethyl)-7-hydroxyl)hepyl)thio)methyl-Sar]-3-cyclosporin
365	S		[(S)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-cyclosporin
366	S		[(S)-(((S)-3-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-cyclosporin
367	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
368	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
369	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
370	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
371	S		[(S)-(((R)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
372	S		[(S)-(((S)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
373	S		[(S)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-cyclosporin
374	S		[(S)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-cyclosporin
375	S		[(S)-(((R)-3-Hydroxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
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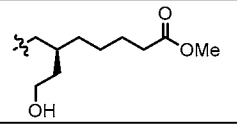
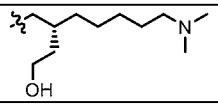
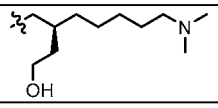
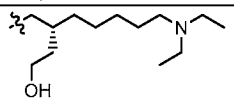
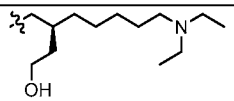
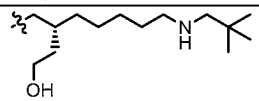
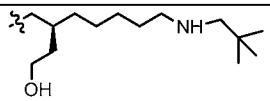
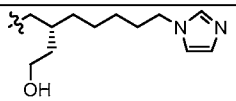
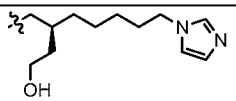
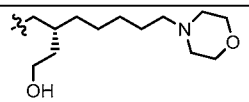
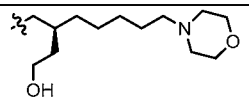
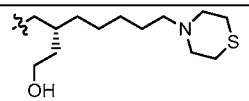
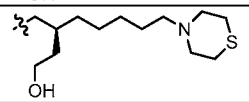
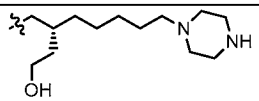
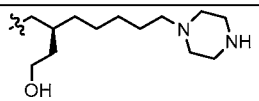
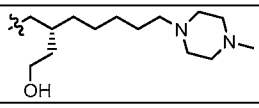
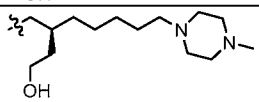
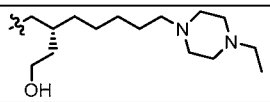
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379	S		[(S)-(((R)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-cyclosporin
380	S		[(S)-(((S)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-cyclosporin
381	S		[(S)-(((R)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
382	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
383	S		[(S)-(((R)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
384	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-cyclosporin
385	S		[(S)-(((R)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-cyclosporin
386	S		[(S)-(((S)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-cyclosporin
387	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-cyclosporin
388	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-cyclosporin
389	S		[(S)-((((R)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-cyclosporin
390	S		[(S)-((((S)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-cyclosporin
391	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-cyclosporin
392	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-cyclosporin
393	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
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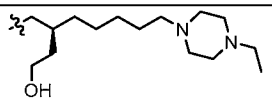
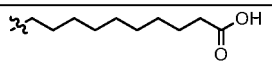
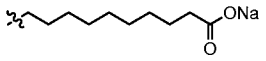
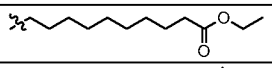
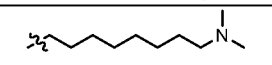
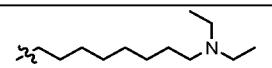
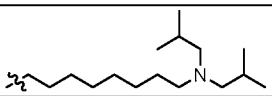
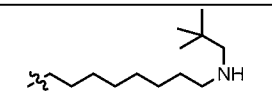
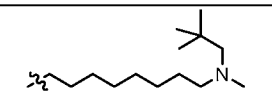
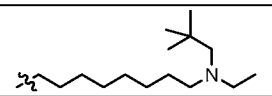
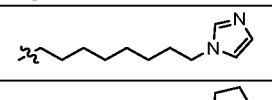
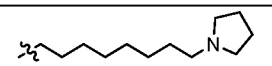
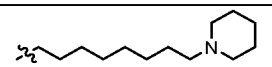
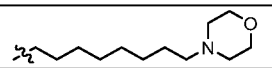
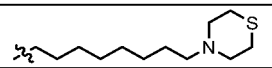
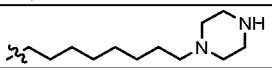
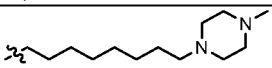
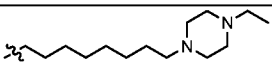
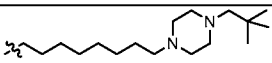
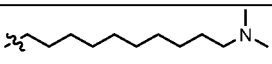
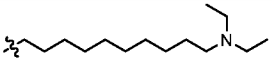
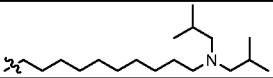
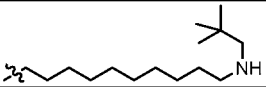
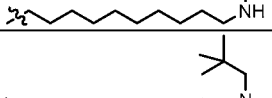
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397	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-cyclosporin
398	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(neopentylamino)hepxyl)thio)methyl-Sar]-3-cyclosporin
399	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-cyclosporin
400	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-cyclosporin
401	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-cyclosporin
402	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-cyclosporin
403	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-cyclosporin
404	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-cyclosporin
405	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-cyclosporin
406	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-cyclosporin
407	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-cyclosporin
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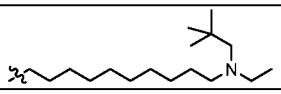
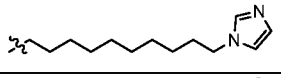
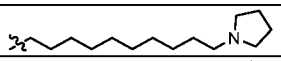
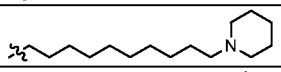
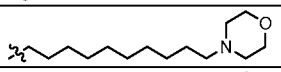
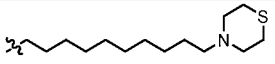
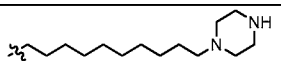
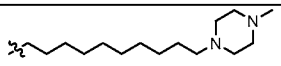
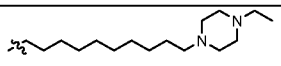
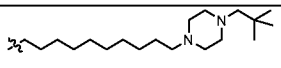
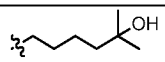
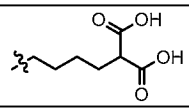
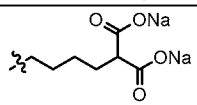
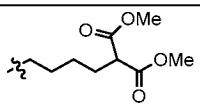
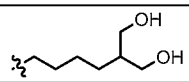
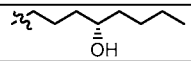
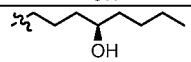
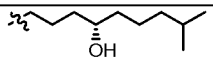
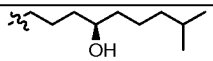
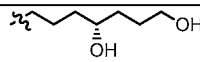
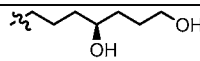
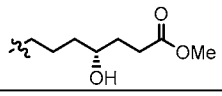
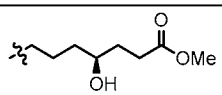
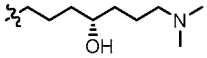
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410	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-cyclosporin
411	S		[(S)-((7-Hydroxy-7-methyloctyl)thio)methyl-Sar]-3-cyclosporin
412	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-cyclosporin
413	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-cyclosporin-disodium salt
414	S		[(S)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)thio)methyl-Sar]-3-cyclosporin
415	S		[(S)-((8-Hydroxy-7-hydroxymethyloctyl)thio)methyl-Sar]-3-cyclosporin
416	S		[(S)-(((S)-4-Hydroxydecyl)thio)methyl-Sar]-3-cyclosporin
417	S		[(S)-(((R)-4-Hydroxydecyl)thio)methyl-Sar]-3-cyclosporin
418	S		[(S)-(((S)-4-Hydroxy-10-methylundecyl)thio)methyl-Sar]-3-cyclosporin
419	S		[(S)-(((R)-4-Hydroxy-10-methylundecyl)thio)methyl-Sar]-3-cyclosporin
420	S		[(S)-(((S)-4,9-Dihydroxynonyl)thio)methyl-Sar]-3-cyclosporin
421	S		[(S)-(((R)-4,9-Dihydroxynonyl)thio)methyl-Sar]-3-cyclosporin
422	S		[(S)-(((S)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-cyclosporin
423	S		[(S)-(((R)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-cyclosporin
424	S		[(S)-(((S)-4-Hydroxy-9-(dimethylamino)nonyl)thio)methyl-Sar]-3-cyclosporin
425	S		[(S)-(((R)-4-Hydroxy-9-(dimethylamino)nonyl)thio)methyl-Sar]-3-cyclosporin
426	S		[(S)-(((S)-4-Hydroxy-9-(diethylamino)nonyl)thio)methyl-Sar]-3-cyclosporin
427	S		[(S)-(((R)-4-Hydroxy-9-(diethylamino)nonyl)thio)methyl-Sar]-3-cyclosporin
428	S		[(S)-(((S)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-cyclosporin
429	S		[(S)-(((R)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-cyclosporin
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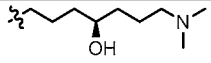
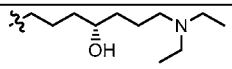
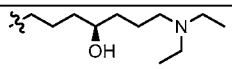
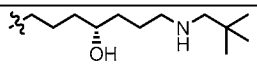
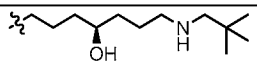
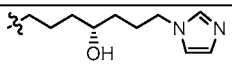
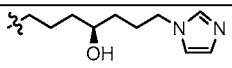
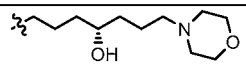
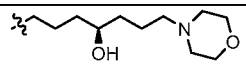
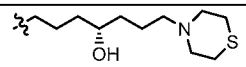
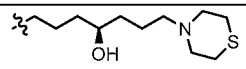
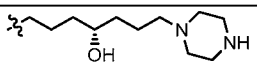
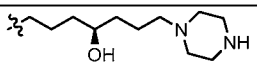
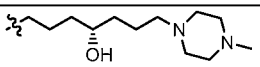
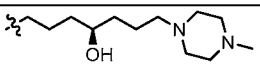
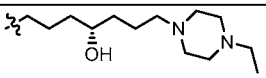
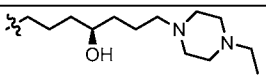
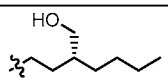
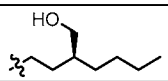
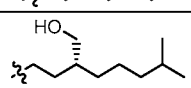
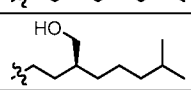
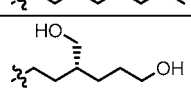
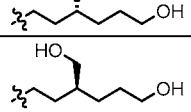
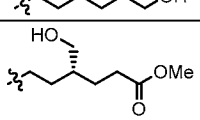
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432	S		[(S)-(((S)-4-Hydroxy-9-morpholinononyl)thio)methyl-Sar]-3-cyclosporin
433	S		[(S)-(((R)-4-Hydroxy-9-morpholinononyl)thio)methyl-Sar]-3-cyclosporin
434	S		[(S)-(((S)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-cyclosporin
435	S		[(S)-(((R)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-cyclosporin
436	S		[(S)-(((S)-4-Hydroxy-9-piperazin-1-ylnonyl)thio)methyl-Sar]-3-cyclosporin
437	S		[(S)-(((R)-4-Hydroxy-9-piperazin-1-ylnonyl)thio)methyl-Sar]-3-cyclosporin
438	S		[(S)-(((S)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-cyclosporin
439	S		[(S)-(((R)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-cyclosporin
440	S		[(S)-(((S)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-cyclosporin
441	S		[(S)-(((R)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyyl)thio)methyl-Sar]-3-cyclosporin
442	S		[(S)-(((R)-3-(Hydroxymethyl)nonyl)thio)methyl-Sar]-3-cyclosporin
443	S		[(S)-(((S)-3-(Hydroxymethyl)nonyl)thio)methyl-Sar]-3-cyclosporin
444	S		[(S)-(((R)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-cyclosporin
445	S		[(S)-(((S)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-cyclosporin
446	S		[(S)-(((R)-3-(Hydroxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-cyclosporin
447	S		[(S)-(((S)-3-(Hydroxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-cyclosporin
448	S		[(S)-(((R)-3-Hydroxymethyl-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-cyclosporin
449	S		[(S)-(((S)-3-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-cyclosporin
450	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-cyclosporin
451	S		[(S)-(((R)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-cyclosporin
452	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-cyclosporin
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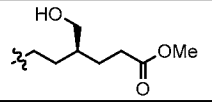
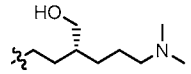
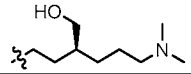
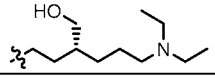
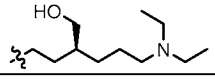
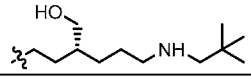
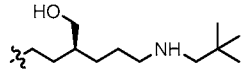
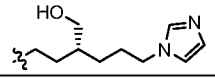
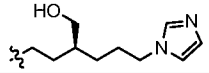
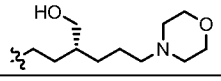
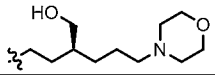
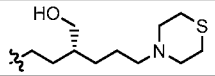
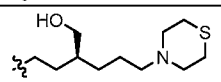
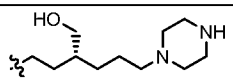
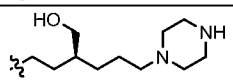
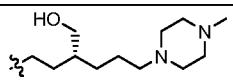
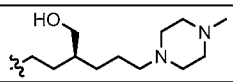
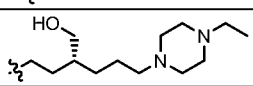
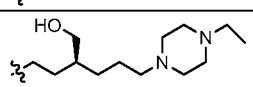
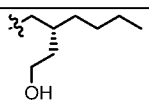
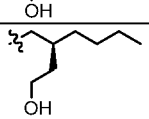
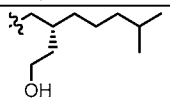
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456	S		[(S)-(((R)-3-Hydroxymethyl-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
457	S		[(S)-(((S)-3-Hydroxymethyl-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
458	S		[(S)-(((R)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-cyclosporin
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460	S		[(S)-(((R)-3-Hydroxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-cyclosporin
461	S		[(S)-(((S)-3-Hydroxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-cyclosporin
462	S		[(S)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-cyclosporin
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464	S		[(S)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
465	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
466	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
467	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-isopropylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-cyclosporin
468	S		[(S)-(((R)-2-(2-Hydroxyethyl)octyl)thio)methyl-Sar]-3-cyclosporin
469	S		[(S)-(((S)-2-(2-Hydroxyethyl)octyl)thio)methyl-Sar]-3-cyclosporin
470	S		[(S)-(((R)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-cyclosporin
471	S		[(S)-(((S)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-cyclosporin
472	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-cyclosporin
473	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-cyclosporin
474	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-cyclosporin

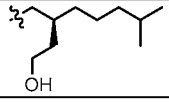
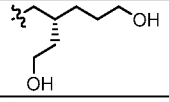
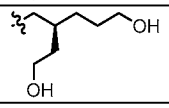
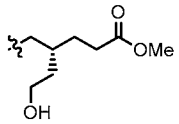
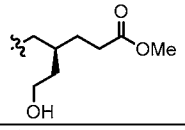
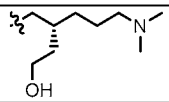
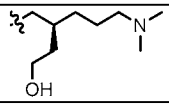
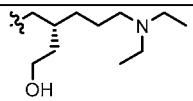
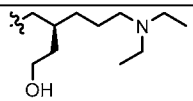
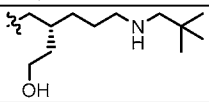
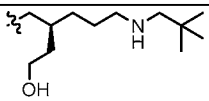
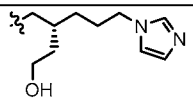
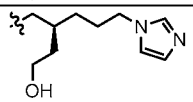
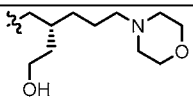
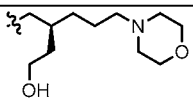
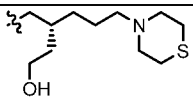
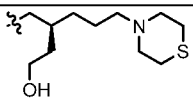
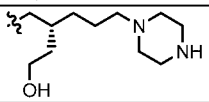
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477	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
478	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
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480	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
481	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-cyclosporin
482	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-cyclosporin
483	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-cyclosporin
484	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
485	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
486	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
487	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-cyclosporin
488	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-cyclosporin
489	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-cyclosporin
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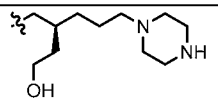
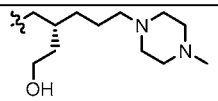
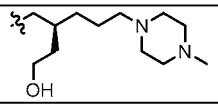
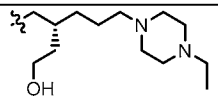
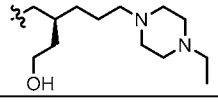
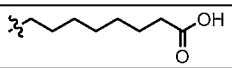
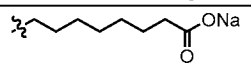
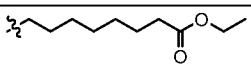
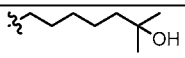
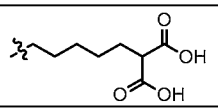
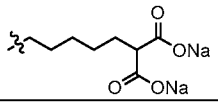
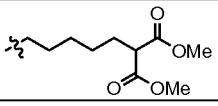
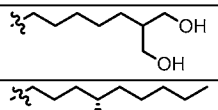
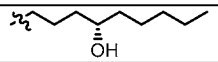
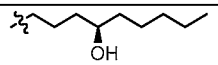
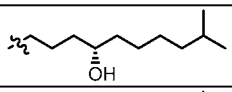
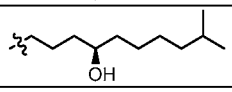
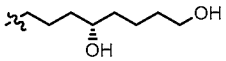
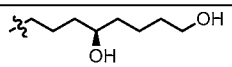
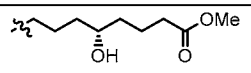
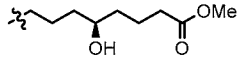
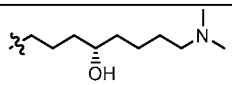
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494	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-cyclosporin
495	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-cyclosporin-potassium salt
496	S		[(S)-(9-(Ethoxycarbonyl)nonylthio)methyl-Sar]-3-cyclosporin
497	O		[(R)-(8-(N,N-Dimethylamino)octyloxy)methyl-Sar]-3-cyclosporin
498	O		[(R)-(8-(N,N-Diethylamino)octyloxy)methyl-Sar]-3-cyclosporin
499	O		[(R)-(8-(N,N-Diisobutylamino)octyloxy)methyl-Sar]-3-cyclosporin
500	O		[(R)-(8-(Neopentylamino)octyloxy)methyl-Sar]-3-cyclosporin
501	O		[(R)-(8-(N-methyl-N-neopentyl)amino)octyloxy)methyl-Sar]-3-cyclosporin
502	O		[(R)-(8-(N-Ethyl-N-neopentyl)amino)octyloxy)methyl-Sar]-3-cyclosporin
503	O		[(R)-(8-(1H-Imidazol-1-yl)octyloxy)methyl-Sar]-3-cyclosporin
504	O		[(R)-(8-(Pyrrolidin-1-yl)octyloxy)methyl-Sar]-3-cyclosporin
505	O		[(R)-(8-(Piperidin-1-yl)octyloxy)methyl-Sar]-3-cyclosporin
506	O		[(R)-((8-Morpholinooctyl)oxy)methyl-Sar]-3-cyclosporin
507	O		[(R)-((8-Thiomorpholinooctyl)oxy)methyl-Sar]-3-cyclosporin
508	O		[(R)-((8-(Piperazin-1-yl)octyl)oxy)methyl-Sar]-3-cyclosporin
509	O		[(R)-((8-(4-Methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-cyclosporin
510	O		[(R)-((8-(4-Ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-cyclosporin
511	O		[(R)-((8-(4-Neopentylpiperazin-1-yl)octyloxy)methyl-Sar]-3-cyclosporin
512	O		[(R)-(10-(N,N-Dimethylamino)decyloxy)methyl-Sar]-3-cyclosporin
513	O		[(R)-(10-(N,N-Diethylamino)decyloxy)methyl-Sar]-3-cyclosporin
514	O		[(R)-(10-(N,N-Diisobutylamino)decyloxy)methyl-Sar]-3-cyclosporin
515	O		[(R)-(10-(Neopentylamino)decyloxy)methyl-Sar]-3-cyclosporin
516	O		[(R)-(10-(Methyl(neopentyl)amino)decyloxy)methyl-Sar]-3-cyclosporin

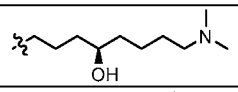
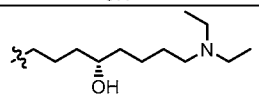
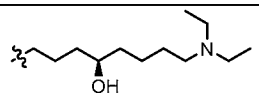
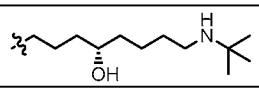
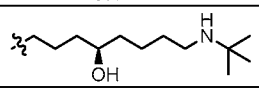
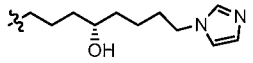
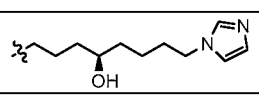
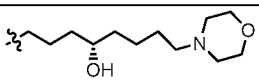
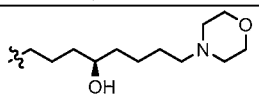
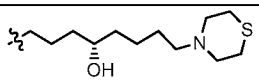
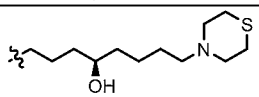
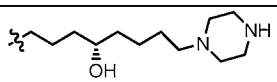
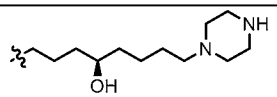
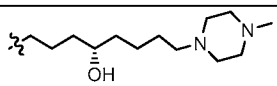
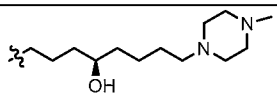
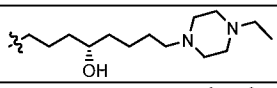
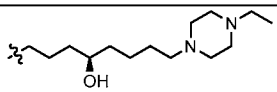
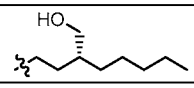
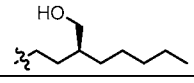
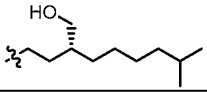
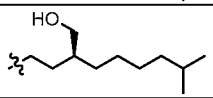
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518	O		[(R)-(10-(1H-imidazol-1-yl)decyloxy)methyl-Sar]-3-cyclosporin
519	O		[(R)-(10-(Pyrrolidin-1-yl)decyloxy)methyl-Sar]-3-cyclosporin
520	O		[(R)-(10-(Piperidin-1-yl)decyloxy)methyl-Sar]-3-cyclosporin
521	O		[(R)-((10-Morpholinodecyl)oxy)methyl-Sar]-3-cyclosporin
522	O		[(R)-((10-Thiomorpholinodecyl)oxy)methyl-Sar]-3-cyclosporin
523	O		[(R)-((10-(Piperazin-1-yl)decyl)oxy)methyl-Sar]-3-cyclosporin
524	O		[(R)-((10-(4-Methylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-cyclosporin
525	O		[(R)-((10-(4-Ethylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-cyclosporin
526	O		[(R)-((10-(4-Neopentylpiperazin-1-yl)decyloxy)methyl-Sar]-3-cyclosporin
527	O		[(R)-((5-Hydroxy-5-methylhexyl)oxy)methyl-Sar]-3-cyclosporin
528	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-cyclosporin
529	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-cyclosporin-disodium salt
530	O		[(R)-((6-Methoxy-5-(methoxycarbonyl)-6-oxohexyl)oxy)methyl-Sar]-3-cyclosporin
531	O		[(R)-((6-Hydroxy-5-hydroxymethylhexyl)oxy)methyl-Sar]-3-cyclosporin
532	O		[(R)-(((S)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-cyclosporin
533	O		[(R)-((R)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-cyclosporin
534	O		[(R)-((S)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-cyclosporin
535	O		[(R)-((R)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-cyclosporin
536	O		[(R)-((S)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-cyclosporin
537	O		[(R)-((R)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-cyclosporin
538	O		[(R)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-cyclosporin
539	O		[(R)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-cyclosporin
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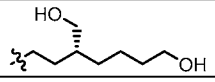
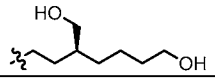
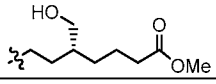
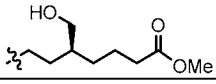
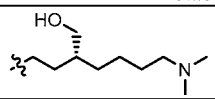
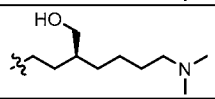
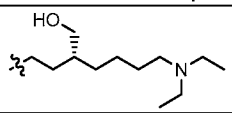
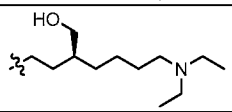
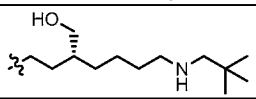
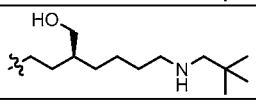
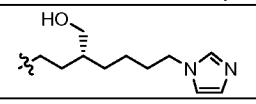
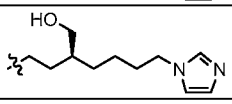
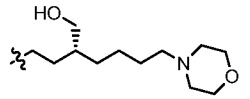
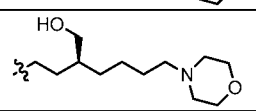
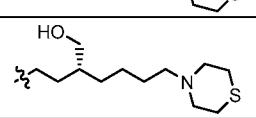
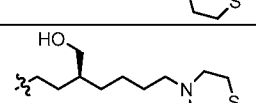
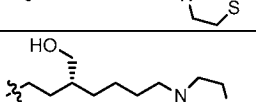
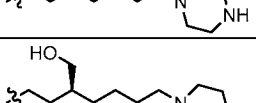
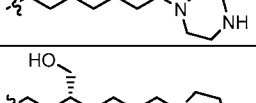
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542	O		[(R)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-cyclosporin
543	O		[(R)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-cyclosporin
544	O		[(R)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-cyclosporin
545	O		[(R)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-cyclosporin
546	O		[(R)-(((S)-4-Hydroxy-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-cyclosporin
547	O		[(R)-(((R)-4-Hydroxy-7-(imidazo-1-yl)heptyl)oxy)methyl-Sar]-3-cyclosporin
548	O		[(R)-(((S)-4-Hydroxy-7-morpholinoheptyl)oxy)methyl-Sar]-3-cyclosporin
549	O		[(R)-(((R)-4-Hydroxy-7-morpholinoheptyl)oxy)methyl-Sar]-3-cyclosporin
550	O		[(R)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-cyclosporin
551	O		[(R)-(((R)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-cyclosporin
552	O		[(R)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-cyclosporin
553	O		[(R)-(((R)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-cyclosporin
554	O		[(R)-(((S)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-cyclosporin
555	O		[(R)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl)heptyl) oxy)methyl-Sar]-3-cyclosporin
556	O		[(R)-(((S)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptylcyclos)oxy)methyl-Sar]-3-cyclosporin
557	O		[(R)-(((R)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-cyclosporin
558	O		[(R)-(((R)-3-(Hydroxymethyl)heptyl)oxy)methyl-Sar]-3-cyclosporin
559	O		[(R)-(((S)-3-(Hydroxymethyl)heptyl)oxy)methyl-Sar]-3-cyclosporin
560	O		[(R)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)oxy)methyl-Sar]-3-cyclosporin
561	O		[(R)-(((S)-3-(Hydroxymethyl)-7-methyloctyl)oxy)methyl-Sar]-3-cyclosporin
562	O		[(R)-(((R)-3-(Hydroxymethyl)-6-hydroxyhexyl)oxy)methyl-Sar]-3-cyclosporin
563	O		[(R)-(((S)-3-(Hydroxymethyl)-6-hydroxyhexyl)oxy)methyl-Sar]-3-cyclosporin
564	O		[(R)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-cyclosporin

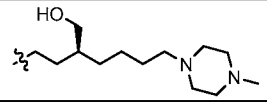
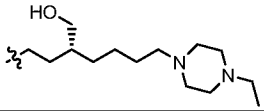
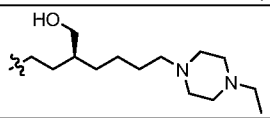
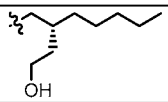
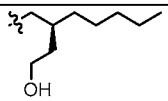
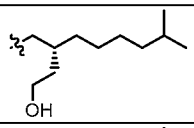
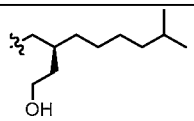
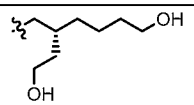
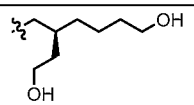
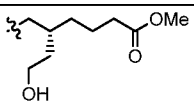
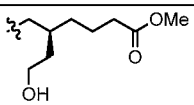
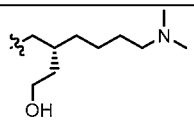
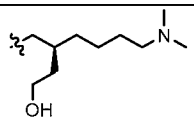
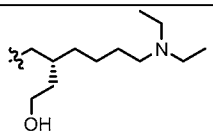
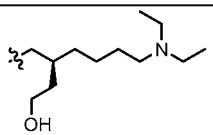
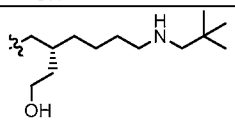
565	O		[(R)-(((S)-3-Hydroxy-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-cyclosporin
566	O		[(R)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-cyclosporin
567	O		[(R)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-cyclosporin
568	O		[(R)-(((R)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-cyclosporin
569	O		[(R)-(((S)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-cyclosporin
570	O		[(R)-(((R)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-cyclosporin
571	O		[(R)-(((S)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-cyclosporin
572	O		[(R)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)oxy)methyl-Sar]-3-cyclosporin
573	O		[(R)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)oxy)methyl-Sar]-3-cyclosporin
574	O		[(R)-(((R)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-cyclosporin
575	O		[(R)-(((S)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-cyclosporin
576	O		[(R)-(((R)-3-Hydroxymethyl-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-cyclosporin
577	O		[(R)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-cyclosporin
578	O		[(R)-(((R)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-cyclosporin
579	O		[(R)-(((S)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-cyclosporin
580	O		[(R)-(((R)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-cyclosporin
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583	O		[(R)-(((S)-3-Hydroxymethyl-6-(4-isopropylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-cyclosporin
584	O		[(R)-(((R)-2-(2-Hydroxyethyl)hexyl)oxy)methyl-Sar]-3-cyclosporin
585	O		[(R)-(((S)-2-(2-Hydroxyethyl)hexyl)oxy)methyl-Sar]-3-cyclosporin
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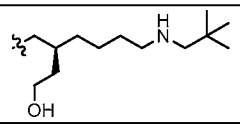
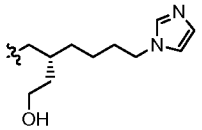
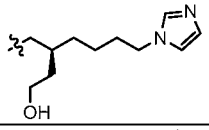
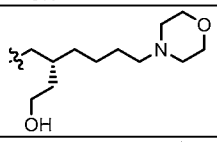
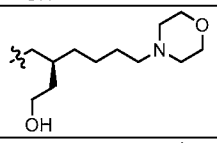
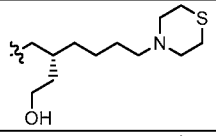
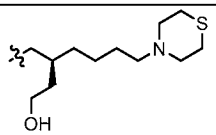
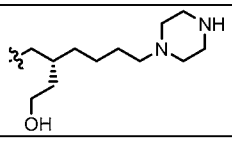
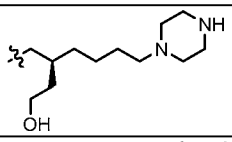
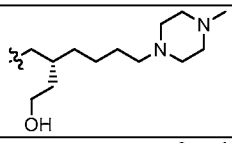
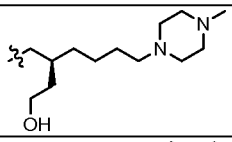
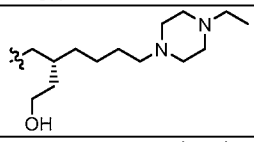
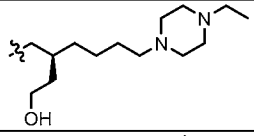
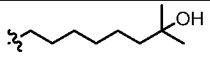
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588	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-cyclosporin
589	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-cyclosporin
590	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-cyclosporin
591	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-cyclosporin
592	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-cyclosporin
593	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-cyclosporin
594	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-cyclosporin
595	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-cyclosporin
596	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)oxy)methyl-Sar]-3-cyclosporin
597	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)oxy)methyl-Sar]-3-cyclosporin
598	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)oxy)methyl-Sar]-3-cyclosporin
599	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)oxy)methyl-Sar]-3-cyclosporin
600	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)oxy)methyl-Sar]-3-cyclosporin
601	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)oxy)methyl-Sar]-3-cyclosporin
602	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)oxy)methyl-Sar]-3-cyclosporin
603	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)oxy)methyl-Sar]-3-cyclosporin
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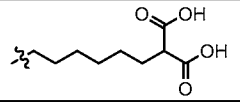
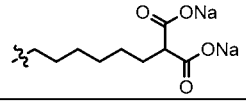
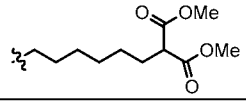
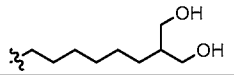
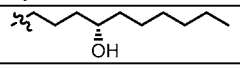
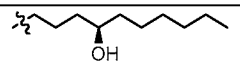
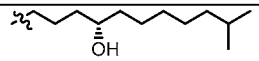
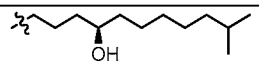
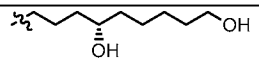
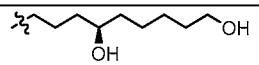
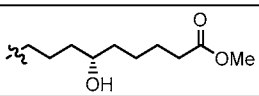
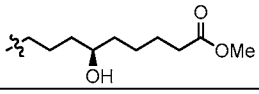
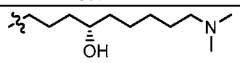
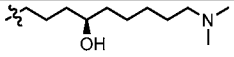
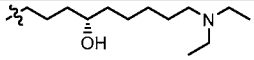
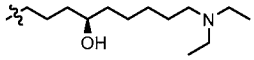
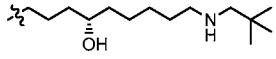
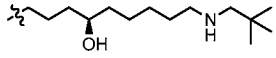
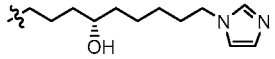
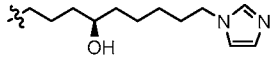
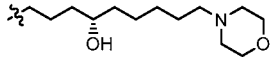
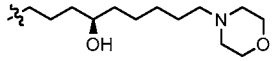
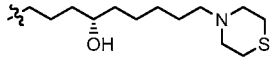
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607	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-cyclosporin
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610	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-cyclosporin
611	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-cyclosporin-sodium salt
612	O		[(R)-(7-(Ethoxycarbonyl)heptyloxy)methyl-Sar]-3-cyclosporin
613	O		[(R)-((6-Hydroxy-6-methylheptyl)oxy)methyl-Sar]-3-cyclosporin
614	O		[(R)-((6,6'-Dicarboxy)hexyloxy)methyl-Sar]-3-cyclosporin
615	O		[(R)-((6,6'-Dicarboxy)hexyloxy)methyl-Sar]-3-cyclosporin-disodium salt
616	O		[(R)-((7-Methoxy-6-(methoxycarbonyl)-7-oxoheptyl)oxy)methyl-Sar]-3-cyclosporin
617	O		[(R)-((7-Hydroxy-6-hydroxymethylheptyl)oxy)methyl-Sar]-3-cyclosporin
618	O		[(R)-((S)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-cyclosporin
619	O		[(R)-((R)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-cyclosporin
620	O		[(R)-((S)-4-Hydroxy-9-methyldecyl)oxy)methyl-Sar]-3-cyclosporin
621	O		[(R)-((R)-4-Hydroxy-9-methyldecyl)oxy)methyl-Sar]-3-cyclosporin
622	O		[(R)-(((S)-4,8-Dihydroxyoctyl)oxy)methyl-Sar]-3-cyclosporin
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625	O		[(R)-(((R)-4-Hydroxy-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-cyclosporin
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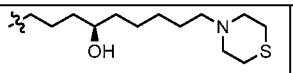
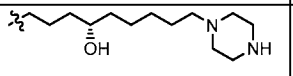
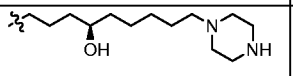
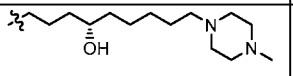
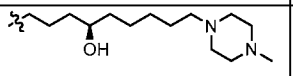
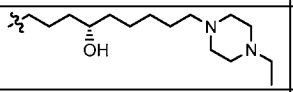
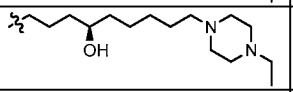
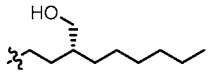
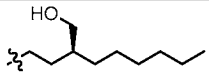
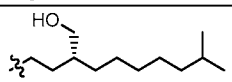
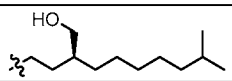
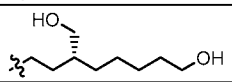
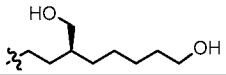
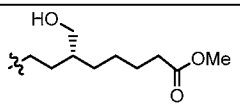
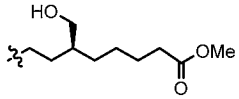
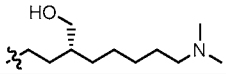
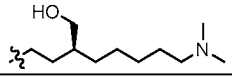
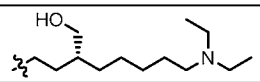
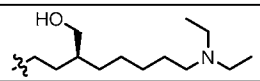
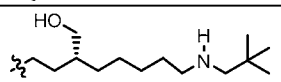
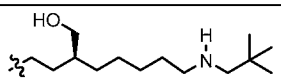
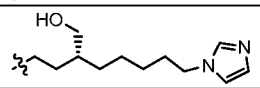
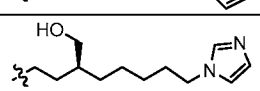
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628	O		[(R)-(((S)-4-Hydroxy-8-(diethylamino)octyl)oxy)methyl-Sar]-3-cyclosporin
629	O		[(R)-(((R)-4-Hydroxy-8-(diethylamino)octyl)oxy)methyl-Sar]-3-cyclosporin
630	O		[(R)-(((S)-4-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-cyclosporin
631	O		[(R)-(((R)-4-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-cyclosporin
632	O		[(R)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)oxy)methyl-Sar]-3-cyclosporin
633	O		[(R)-(((R)-4-Hydroxy-8-(imidazo-1-yl)octyl)oxy)methyl-Sar]-3-cyclosporin
634	O		[(R)-(((S)-4-Hydroxy-8-morpholinooctyl)oxy)methyl-Sar]-3-cyclosporin
635	O		[(R)-(((R)-4-Hydroxy-8-morpholinooctyl)oxy)methyl-Sar]-3-cyclosporin
636	O		[(R)-(((S)-4-Hydroxy-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-cyclosporin
637	O		[(R)-(((R)-4-Hydroxy-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-cyclosporin
638	O		[(R)-(((S)-4-Hydroxy-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-cyclosporin
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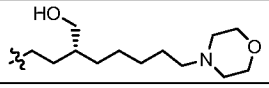
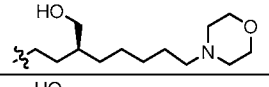
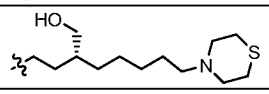
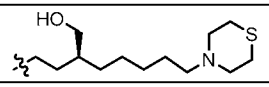
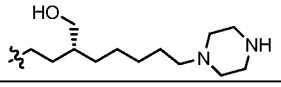
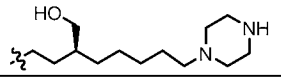
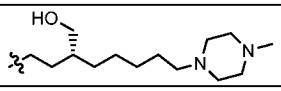
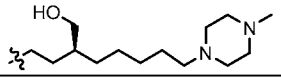
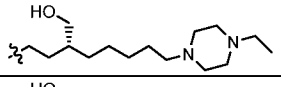
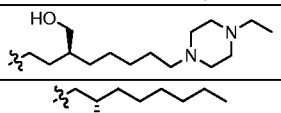
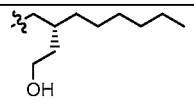
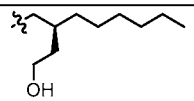
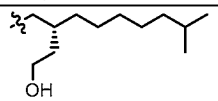
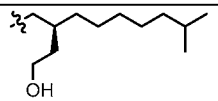
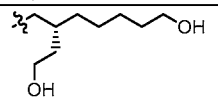
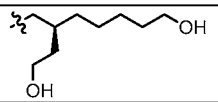
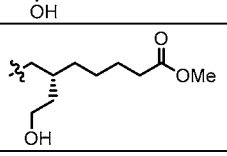
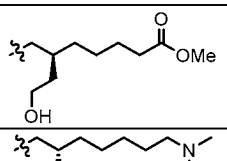
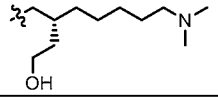
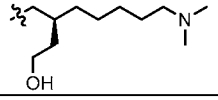
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650	O		[(R)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-cyclosporin
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656	O		[(R)-(((R)-3-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-cyclosporin
657	O		[(R)-(((S)-3-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-cyclosporin
658	O		[(R)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-cyclosporin
659	O		[(R)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)oxy)methyl-Sar]-3-cyclosporin
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699	O		[(R)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)oxy)methyl-Sar]-3-cyclosporin
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701	O		[(R)-(((S)-4-Hydroxydecyl)oxy)methyl-Sar]-3-cyclosporin
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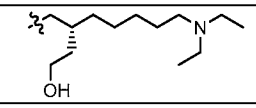
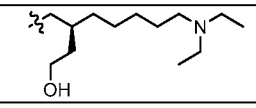
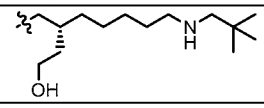
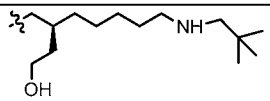
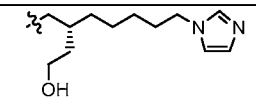
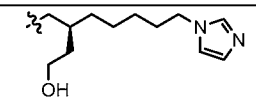
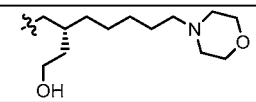
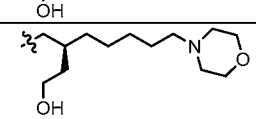
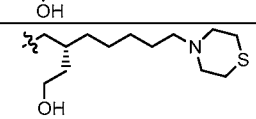
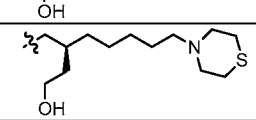
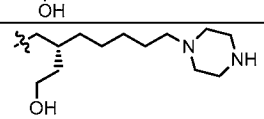
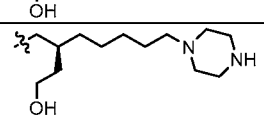
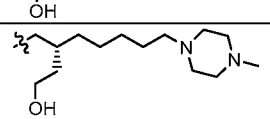
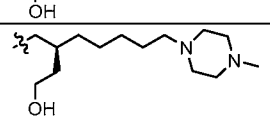
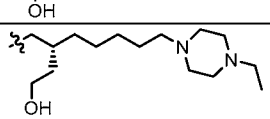
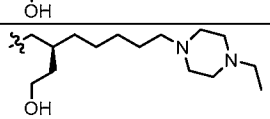
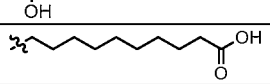
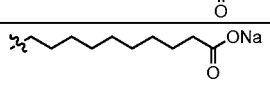
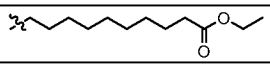
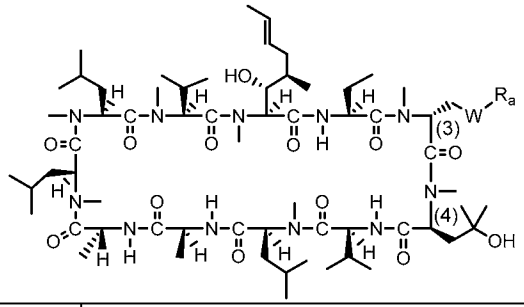
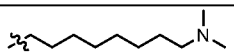
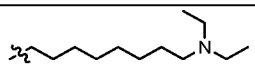
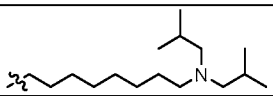
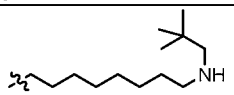
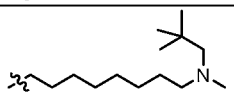
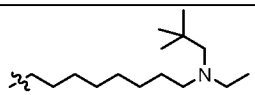
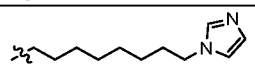
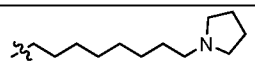
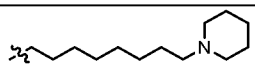
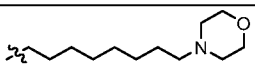
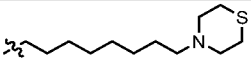
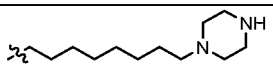
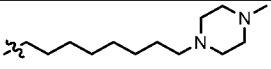
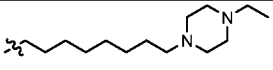
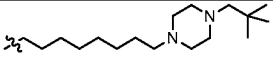
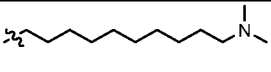
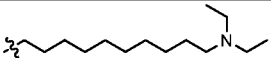
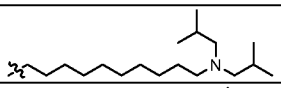
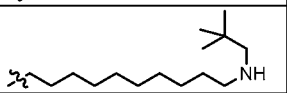
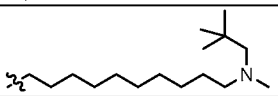
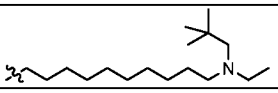
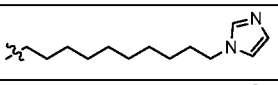
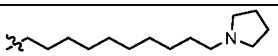
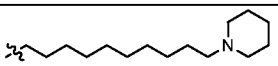
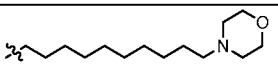
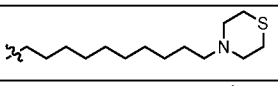
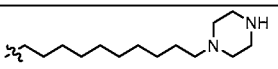
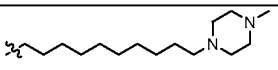
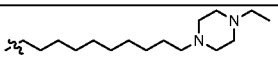
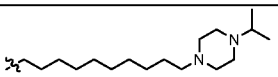
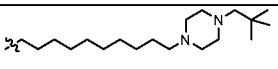
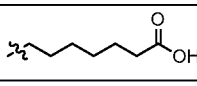
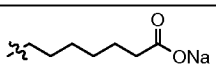
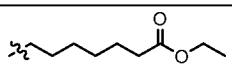
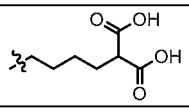
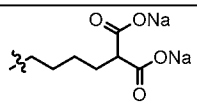
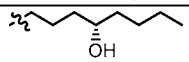
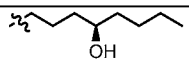
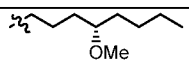
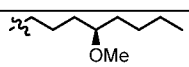
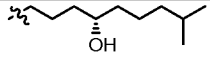
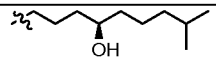
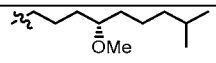
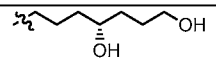
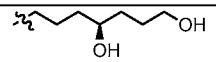
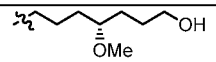
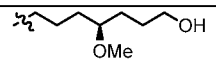
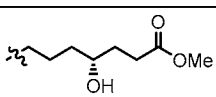
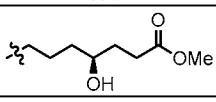
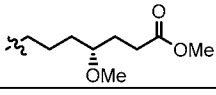
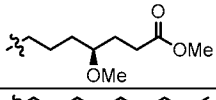
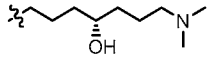
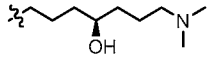
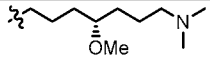
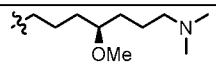
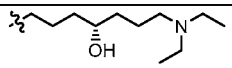
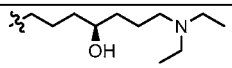
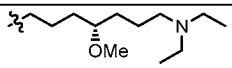
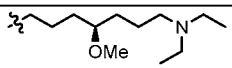
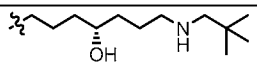
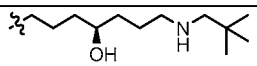
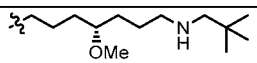
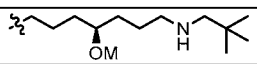
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767	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-cyclosporin
768	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-cyclosporin
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779	O		[(R)-(9-Carboxynonyloxy)methyl-Sar]-3-cyclosporin
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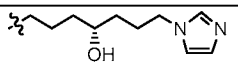
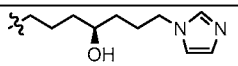
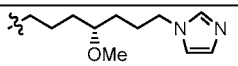
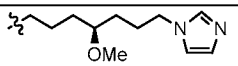
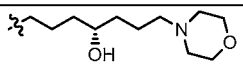
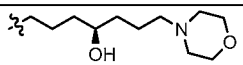
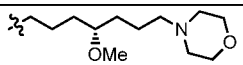
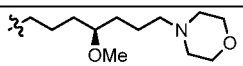
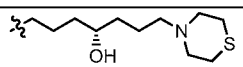
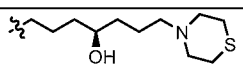
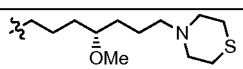
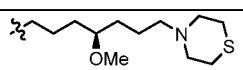
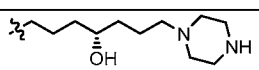
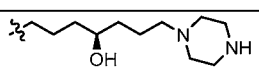
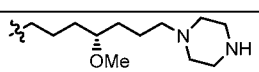
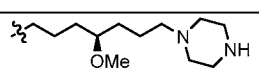
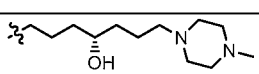
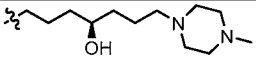
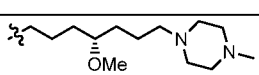
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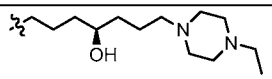
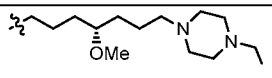
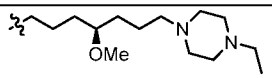
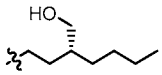
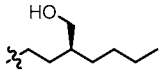
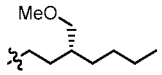
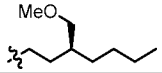
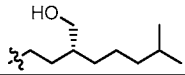
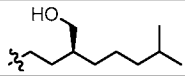
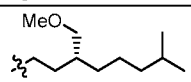
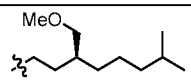
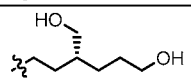
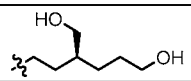
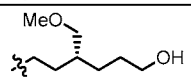
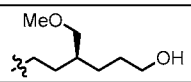
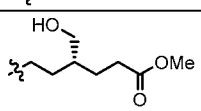
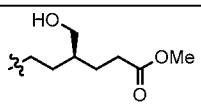
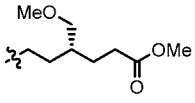
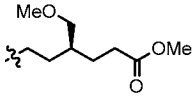
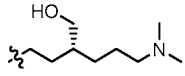


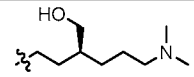
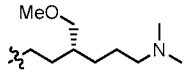
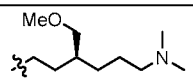
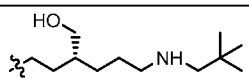
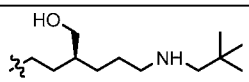
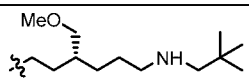
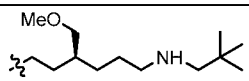
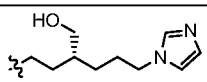
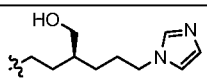
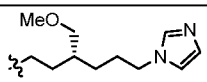
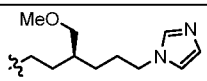
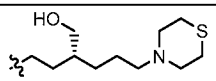
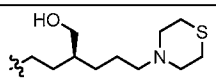
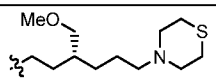
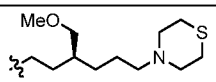
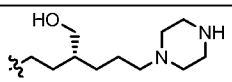
Ex. No.	W	R_a	Name
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783	S		[(S)-(8-(N,N-Diethylamino)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
784	S		[(S)-(8-(N,N-Diisobutylamino)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
785	S		[(S)-(8-(Neopentylamino)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
786	S		[(S)-(8-(N-Methyl-N-neopentyl)amino)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
787	S		[(S)-(8-(N-Ethyl-N-neopentyl)amino)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
788	S		[(S)-(8-(1H-Imidazol-1-yl)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
789	S		[(S)-(8-(Pyrrolidin-1-yl)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
790	S		[(S)-(8-(Piperidin-1-yl)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
791	S		[(S)-((8-Morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
792	S		[(S)-((8-Thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
793	S		[(S)-((8-(Piperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
794	S		[(S)-((8-(4-Methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
795	S		[(S)-((8-(4-Ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
796	S		[(S)-((8-(4-Neopentylpiperazin-1-yl)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
797	S		[(S)-(10-(N,N-Dimethylamino)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
798	S		[(S)-(10-(N,N-Diethylamino)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

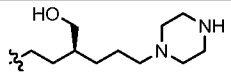
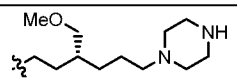
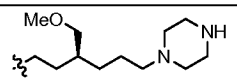
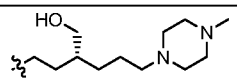
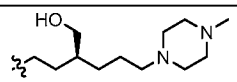
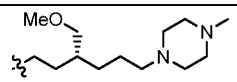
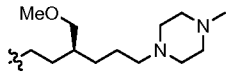
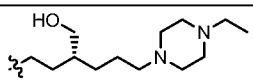
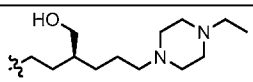
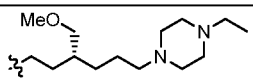
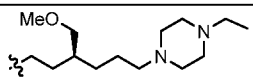
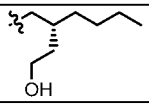
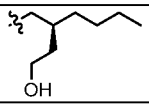
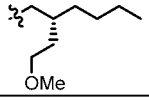
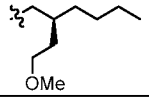
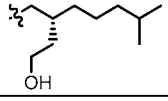
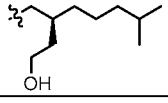
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800	S		[(S)-(10-(Neopentylamino)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
801	S		[(S)-(10-(Methyl(neopentyl)amino)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
802	S		[(S)-(10-(Ethyl(neopentyl)amino)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
803	S		[(S)-(10-(1H-imidazol-1-yl)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
804	S		[(S)-(10-(Pyrrolidin-1-yl)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
805	S		[(S)-(10-(Piperidin-1-yl)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
806	S		[(S)-((10-Morpholinodecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
807	S		[(S)-((10-Thiomorpholinodecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
808	S		[(S)-((10-(Piperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
809	S		[(S)-((10-(4-Methylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
810	S		[(S)-((10-(4-Ethylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
811	S		[(S)-((10-(4-Isopropylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
812	S		[(S)-((10-(4-Neopentylpiperazin-1-yl)decylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
813	S		[(S)-(6-Carboxyhexylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
814	S		[(S)-(6-Carboxyhexylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-sodium salt
815	S		[(S)-(6-(Ethoxycarbonyl)hexylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
816	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
817	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-disodium salt
818	S		[(S)-((S)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
819	S		[(S)-((R)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
820	S		[(S)-((S)-(4-Methoxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
821	S		[(S)-((R)-(4-Methoxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

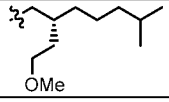
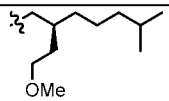
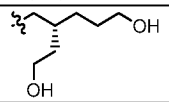
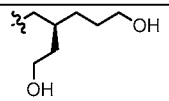
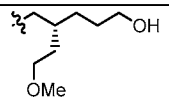
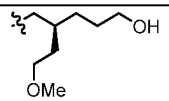
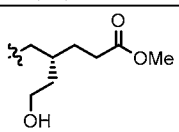
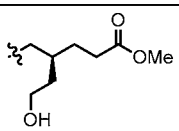
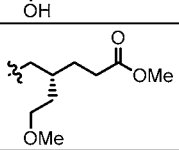
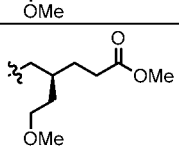
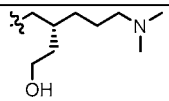
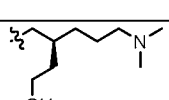
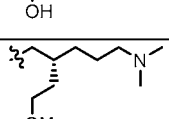
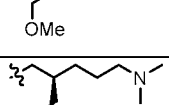
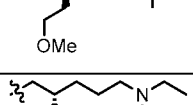
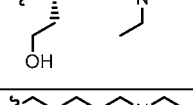
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823	S		[(S)-((R)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
824	S		[(S)-((S)-4-Methoxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
825	S		[(S)-((R)-4-Methoxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
826	S		[(S)-((S)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
827	S		[(S)-((R)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
828	S		[(S)-((S)-4-Methoxy-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
829	S		[(S)-((R)-4-Methoxy-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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832	S		[(S)-(((S)-4-Methoxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
833	S		[(S)-(((R)-4-Methoxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
834	S		[(S)-(((S)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
835	S		[(S)-(((R)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
836	S		[(S)-(((S)-4-Methoxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
837	S		[(S)-(((R)-4-Methoxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
838	S		[(S)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
839	S		[(S)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
840	S		[(S)-(((S)-4-Methoxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
841	S		[(S)-(((R)-4-Methoxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
842	S		[(S)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
843	S		[(S)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
844	S		[(S)-(((S)-4-Methoxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
845	S		[(S)-(((R)-4-Methoxy-7-(neopentylamino)heptyl)thio)methyl-

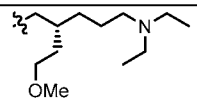
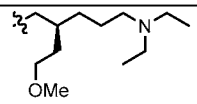
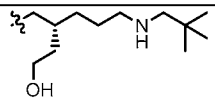
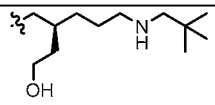
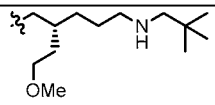
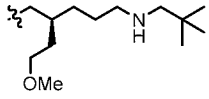
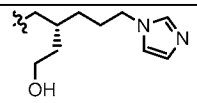
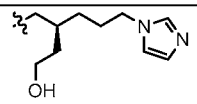
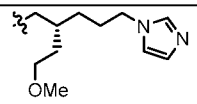
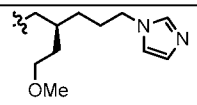
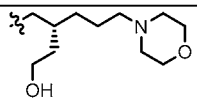
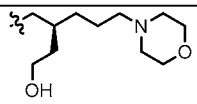
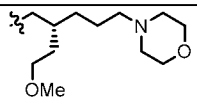
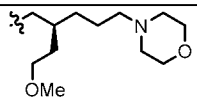
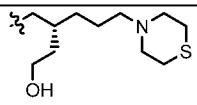
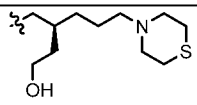
			Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
846	S		[(S)-(((S)-4-Hydroxy-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
847	S		[(S)-(((R)-4-Hydroxy-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
848	S		[(S)-(((S)-4-Methoxy-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
849	S		[(S)-(((R)-4-Methoxy-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
850	S		[(S)-(((S)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
851	S		[(S)-(((R)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
852	S		[(S)-(((S)-4-Methoxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
853	S		[(S)-(((R)-4-Methoxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
854	S		[(S)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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858	S		[(S)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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863	S		[(S)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
864	S		[(S)-(((S)-4-Methoxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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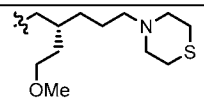
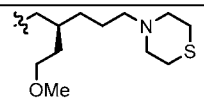
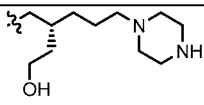
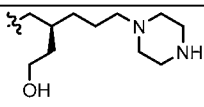
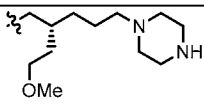
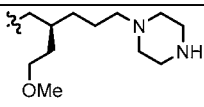
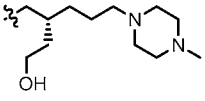
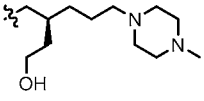
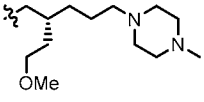
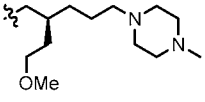
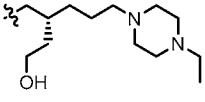
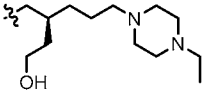
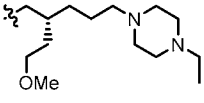
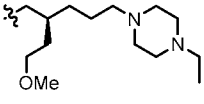
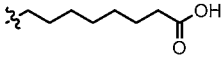
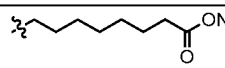
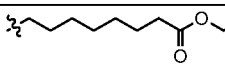
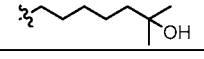
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868	S		[(S)-(((S)-4-Methoxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
869	S		[(S)-(((R)-4-Methoxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
870	S		[(S)-(((R)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
871	S		[(S)-(((S)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
872	S		[(S)-(((R)-3-(Methoxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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877	S		[(S)-(((S)-3-(Methoxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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882	S		[(S)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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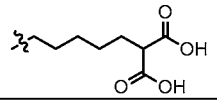
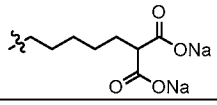
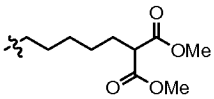
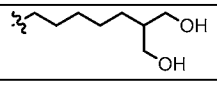
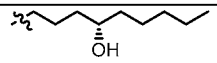
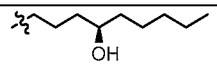
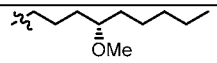
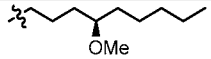
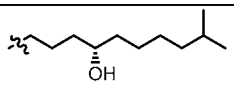
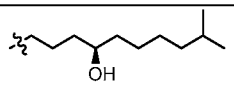
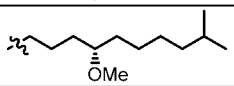
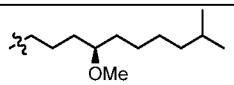
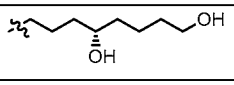
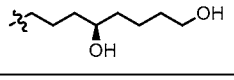
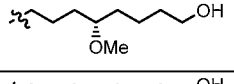
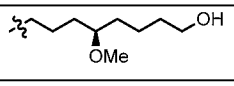
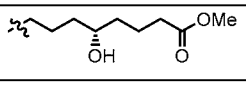
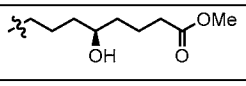
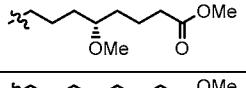
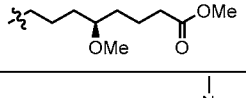
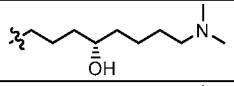
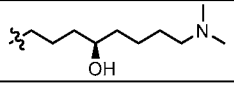
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888	S		[(S)-(((R)-3-(Methoxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
889	S		[(S)-(((S)-3-(Methoxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
890	S		[(S)-(((R)-3-Hydroxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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892	S		[(S)-(((R)-3-Methoxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
893	S		[(S)-(((S)-3-Methoxymethyl-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
894	S		[(S)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
895	S		[(S)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
896	S		[(S)-(((R)-3-Methoxymethyl-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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898	S		[(S)-(((R)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
899	S		[(S)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
900	S		[(S)-(((R)-3-Methoxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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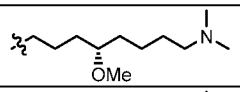
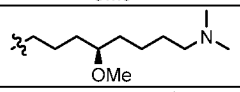
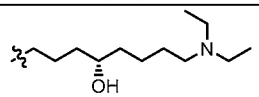
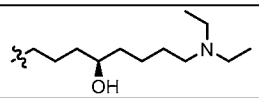
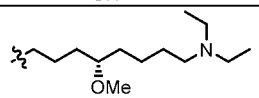
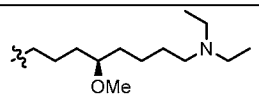
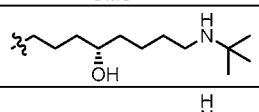
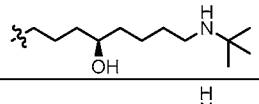
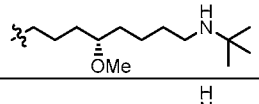
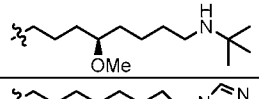
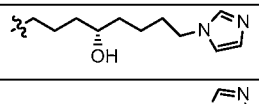
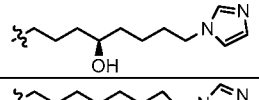
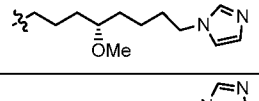
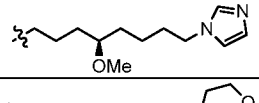
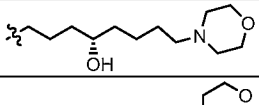
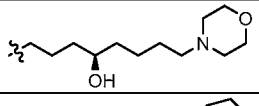
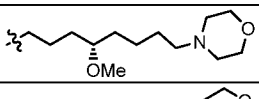
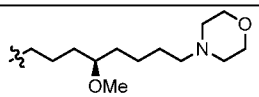
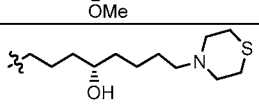
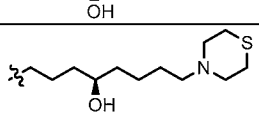
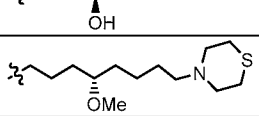
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904	S		[(S)-(((R)-3-Methoxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
905	S		[(S)-(((S)-3-Methoxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
906	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
907	S		[(S)-(((S)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
908	S		[(S)-(((R)-3-Methoxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
909	S		[(S)-(((S)-3-Methoxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
910	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
911	S		[(S)-(((S)-3-Hydroxymethyl-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
912	S		[(S)-(((R)-3-(Methoxymethyl)-6-(4-ethylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
913	S		[(S)-(((S)-3-(Methoxymethyl)-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
914	S		[(S)-(((R)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
915	S		[(S)-(((S)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
916	S		[(S)-(((R)-2-(2-Methoxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
917	S		[(S)-(((S)-2-(2-Methoxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
918	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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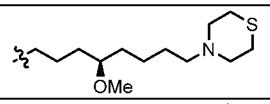
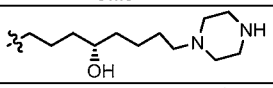
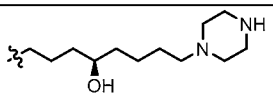
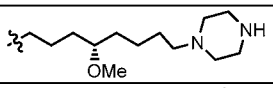
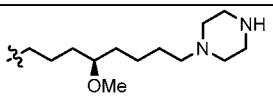
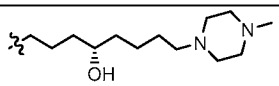
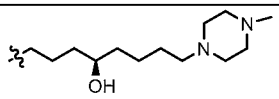
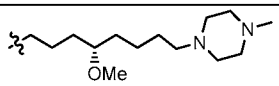
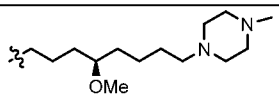
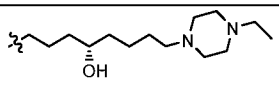
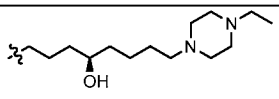
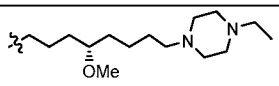
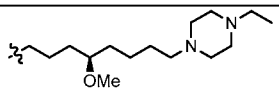
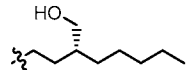
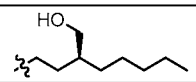
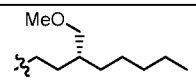
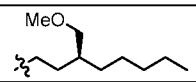
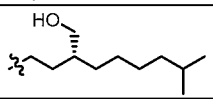
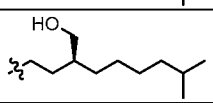
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921	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
922	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
923	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
924	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
925	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
926	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
927	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
928	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
929	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
930	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
931	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
932	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
933	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
934	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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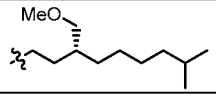
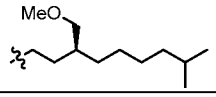
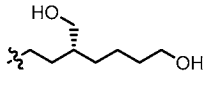
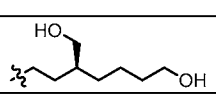
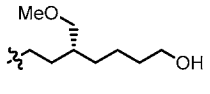
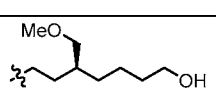
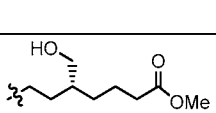
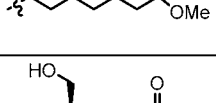
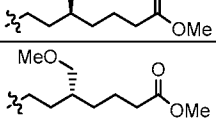
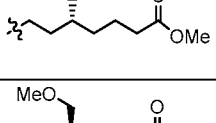
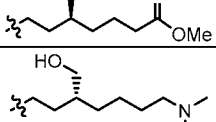
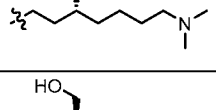
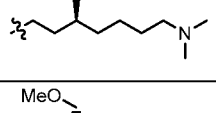
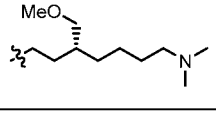
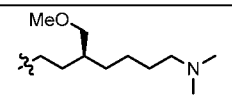
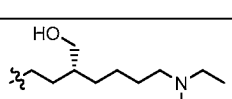
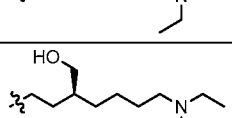
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937	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
938	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
939	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
940	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
941	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
942	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
943	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
944	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
945	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
946	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
947	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
948	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
949	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
950	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
951	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

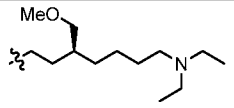
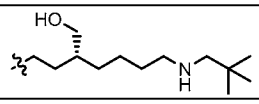
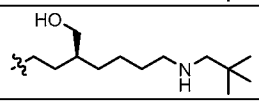
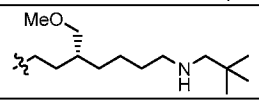
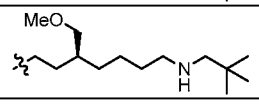
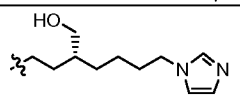
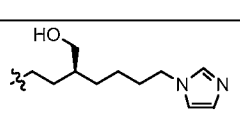
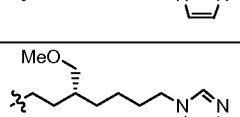
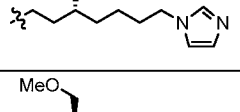
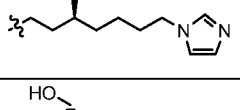
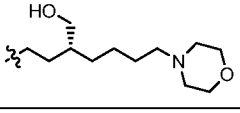
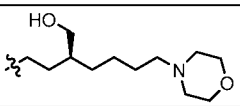
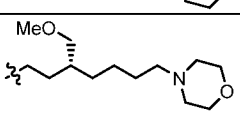
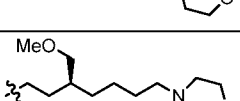
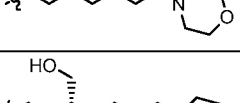
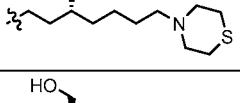
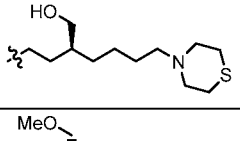
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953	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
954	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
955	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
956	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
957	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
958	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
959	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
960	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
961	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
962	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
963	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
964	S		[(S)-(((R)-2-(2-Methoxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
965	S		[(S)-(((S)-2-(2-Methoxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
966	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
967	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-sodium salt
968	S		[(S)-(7-(Ethoxycarbonyl)heptylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
969	S		[(S)-((6-Hydroxy-6-methylheptyl)thio)methyl-Sar]-3-[(γ-

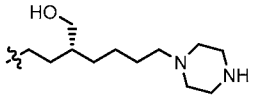
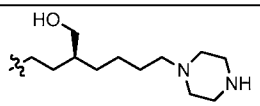
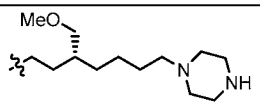
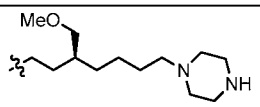
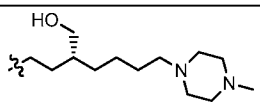
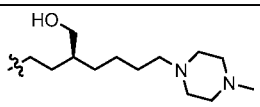
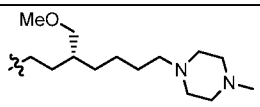
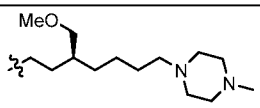
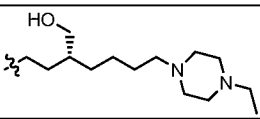
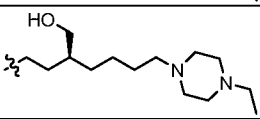
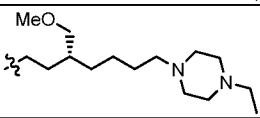
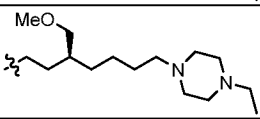
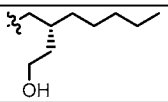
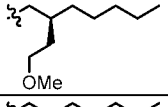
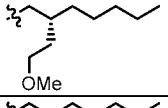
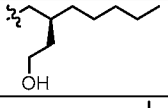
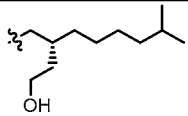
			hydroxy)-N-MeLeu]-4-cyclosporin
970	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
971	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin- disodium salt
972	S		[(S)-((7-Methoxy-6-(methoxycarbonyl)-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
973	S		[(S)-((7-Hydroxy-6-hydroxymethylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
974	S		[(S)-((S)-(4-Hydroxynonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
975	S		[(S)-((R)-(4-Hydroxynonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
976	S		[(S)-((S)-(4-Methoxynonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
977	S		[(S)-((R)-(4-Methoxynonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
978	S		[(S)-((S)-4-Hydroxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
979	S		[(S)-((R)-4-Hydroxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
980	S		[(S)-((S)-4-Methoxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
981	S		[(S)-((R)-4-Methoxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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989	S		[(S)-(((R)-4-Methoxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
990	S		[(S)-(((S)-4-Hydroxy-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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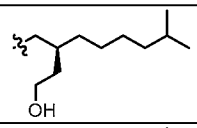
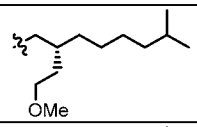
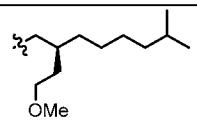
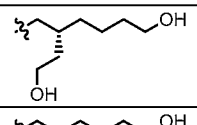
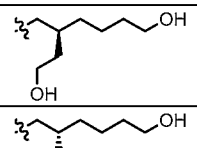
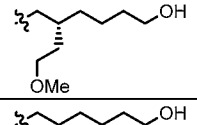
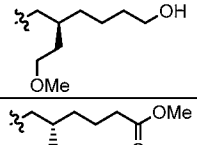
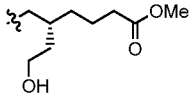
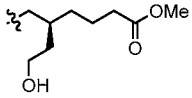
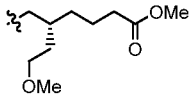
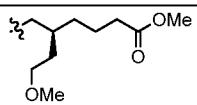
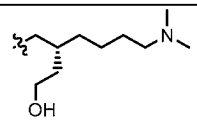
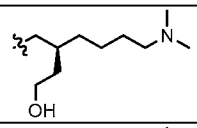
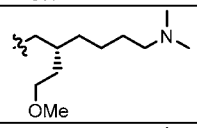
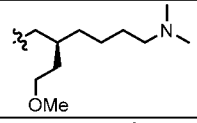
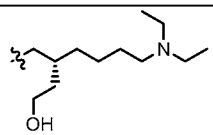
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993	S		[(S)-(((R)-4-Methoxy-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
994	S		[(S)-(((S)-4-Hydroxy-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
995	S		[(S)-(((R)-4-Hydroxy-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
996	S		[(S)-(((S)-4-Methoxy-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
997	S		[(S)-(((R)-4-Methoxy-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
998	S		[(S)-(((S)-4-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
999	S		[(S)-(((R)-4-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1000	S		[(S)-(((S)-4-Methoxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1001	S		[(S)-(((R)-4-Methoxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1002	S		[(S)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1003	S		[(S)-(((R)-4-Hydroxy-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1004	S		[(S)-(((S)-4-Methoxy-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1005	S		[(S)-(((R)-4-Methoxy-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1006	S		[(S)-(((S)-4-Hydroxy-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1007	S		[(S)-(((R)-4-Hydroxy-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1009	S		[(S)-(((R)-4-Methoxy-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1010	S		[(S)-(((S)-4-Hydroxy-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1011	S		[(S)-(((R)-4-Hydroxy-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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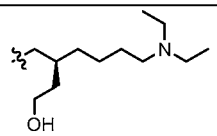
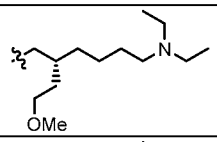
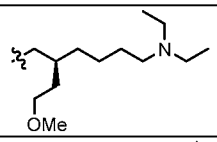
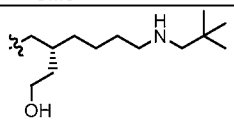
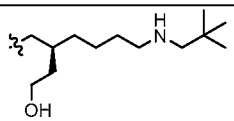
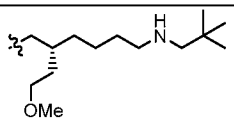
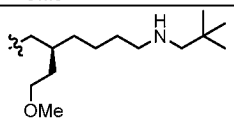
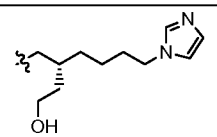
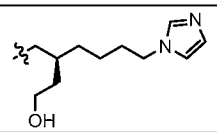
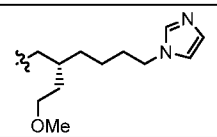
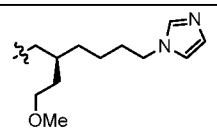
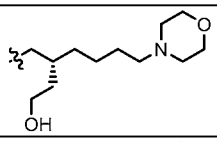
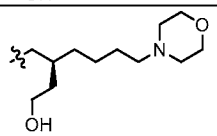
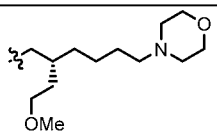
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1014	S		[(S)-(((S)-4-Hydroxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1015	S		[(S)-(((R)-4-Hydroxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1016	S		[(S)-(((S)-4-Methoxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1017	S		[(S)-(((R)-4-Methoxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1018	S		[(S)-(((S)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1019	S		[(S)-(((R)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1020	S		[(S)-(((S)-4-Methoxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1021	S		[(S)-(((R)-4-Methoxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1022	S		[(S)-(((S)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1023	S		[(S)-(((R)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1024	S		[(S)-(((S)-4-Methoxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1025	S		[(S)-(((R)-4-Methoxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1026	S		[(S)-(((R)-3-(Hydroxymethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1027	S		[(S)-(((S)-3-(Hydroxymethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1028	S		[(S)-(((R)-3-(Methoxymethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1029	S		[(S)-(((S)-3-(Methoxymethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1030	S		[(S)-(((R)-3-(Hydroxymethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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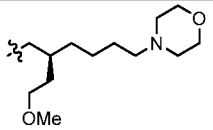
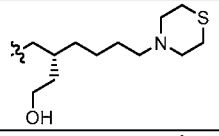
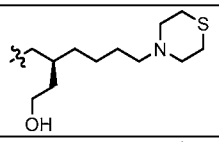
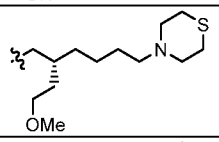
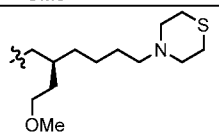
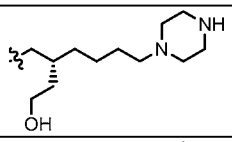
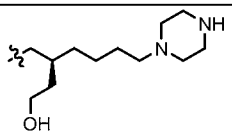
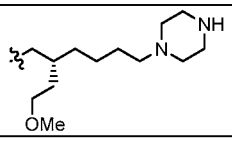
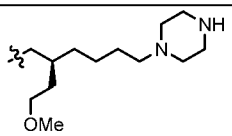
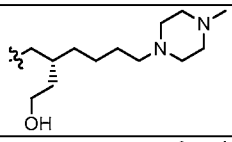
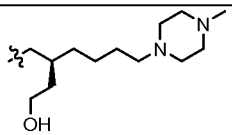
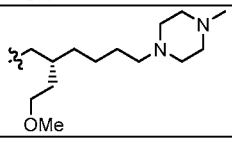
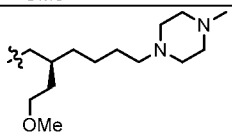
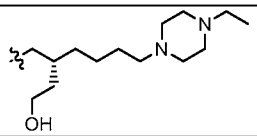
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1034	S		[(S)-((((R)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1035	S		[(S)-((((S)-3-(Hydroxymethyl)-7-hydroxyl)hepyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1037	S		[(S)-((((S)-3-(Methoxymethyl)-7-hydroxyl)hepyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1038	S		[(S)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1039	S		[(S)-(((S)-3-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1040	S		[(S)-(((R)-3-Methoxymethyl-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1041	S		[(S)-(((S)-3-Methoxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1042	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1043	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1044	S		[(S)-((((R)-3-(Methoxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1045	S		[(S)-((((S)-3-(Methoxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1046	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1047	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1048	S		[(S)-((((R)-3-(Methoxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

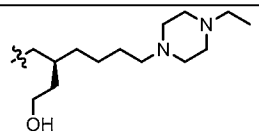
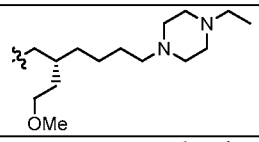
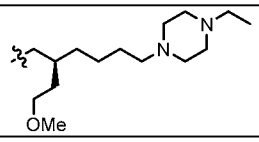
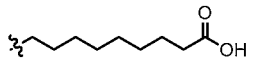
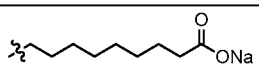
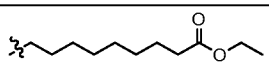
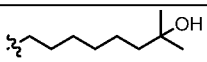
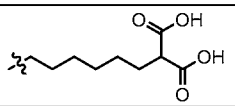
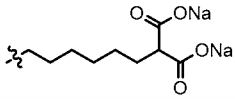
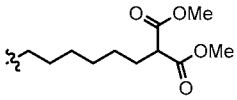
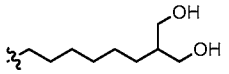
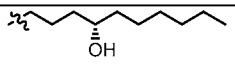
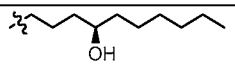
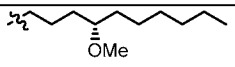
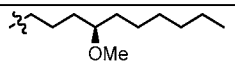
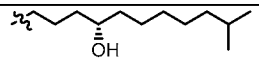
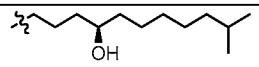
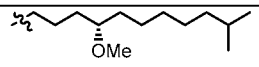
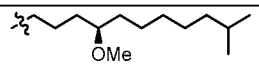
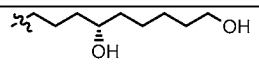
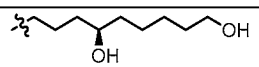
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1050	S		[(S)-(((R)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1051	S		[(S)-(((S)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1052	S		[(S)-(((R)-3-Methoxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1053	S		[(S)-(((S)-3-Methoxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1054	S		[(S)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1055	S		[(S)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1056	S		[(S)-(((R)-3-Methoxymethyl-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1057	S		[(S)-(((S)-3-Methoxymethyl-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1058	S		[(S)-(((R)-3-Hydroxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1059	S		[(S)-(((S)-3-Hydroxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1060	S		[(S)-(((R)-3-Methoxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1061	S		[(S)-(((S)-3-Methoxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1062	S		[(S)-(((R)-3-Hydroxymethyl-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1064	S		[(S)-(((R)-3-Methoxymethyl-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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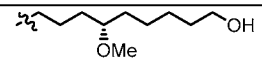
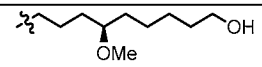
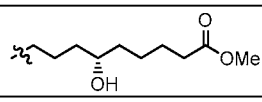
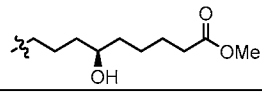
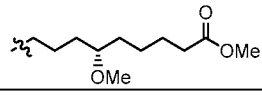
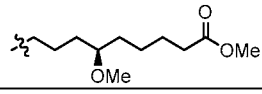
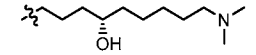
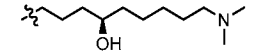
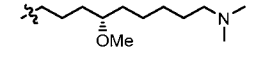
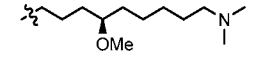
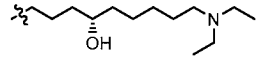
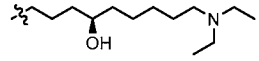
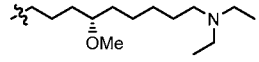
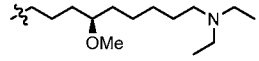
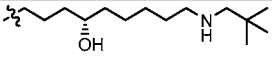
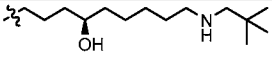
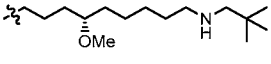
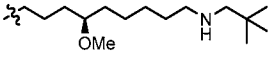
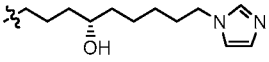
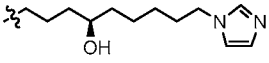
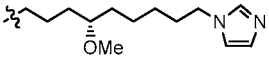
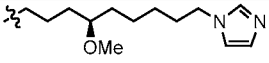
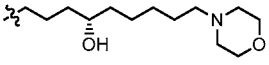
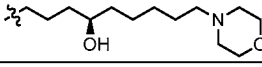
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1067	S		[(S)-(((S)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1068	S		[(S)-(((R)-3-Methoxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1069	S		[(S)-(((S)-3-Methoxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1070	S		[(S)-(((R)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1071	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1072	S		[(S)-(((R)-3-Methoxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1073	S		[(S)-(((S)-3-Methoxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1074	S		[(S)-(((R)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1075	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1076	S		[(S)-(((R)-3-Methoxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1077	S		[(S)-(((S)-3-Methoxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1078	S		[(S)-(((R)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1079	S		[(S)-(((S)-2-(2-Methoxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1080	S		[(S)-(((R)-2-(2-Methoxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1081	S		[(S)-(((S)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1082	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

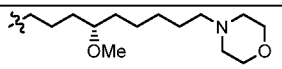
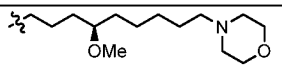
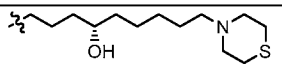
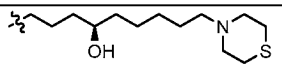
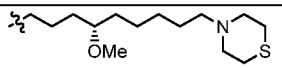
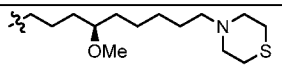
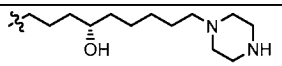
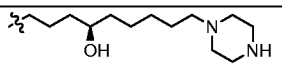
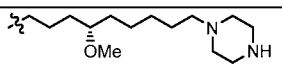
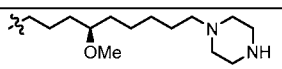
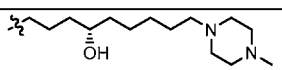
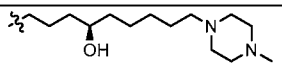
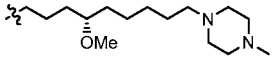
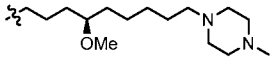
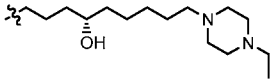
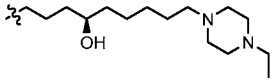
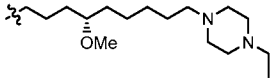
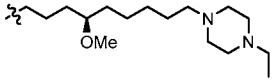
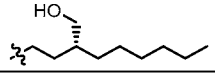
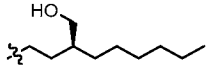
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1084	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1085	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1086	S		[(S)-((((R)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1087	S		[(S)-((((S)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1088	S		[(S)-((((R)-2-(2-Methoxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1089	S		[(S)-((((S)-2-(2-Methoxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1090	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1091	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1092	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1093	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1094	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1095	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1096	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1097	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1098	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

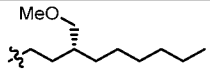
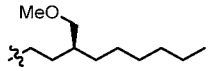
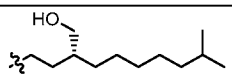
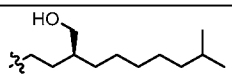
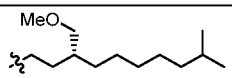
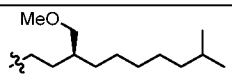
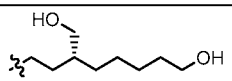
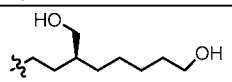
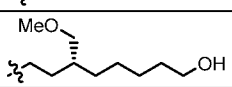
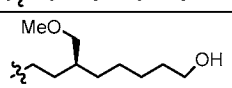
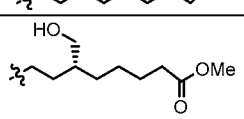
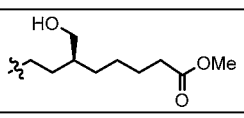
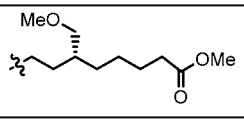
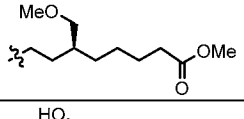
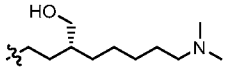
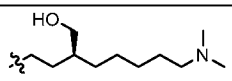
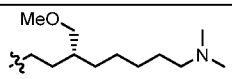
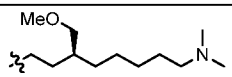
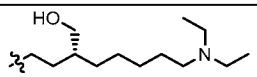
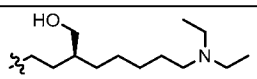
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1100	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1101	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1102	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1103	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1104	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1105	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1106	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1107	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1108	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1109	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1110	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1111	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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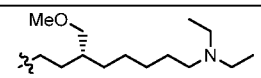
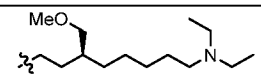
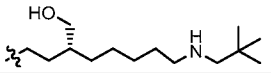
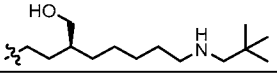
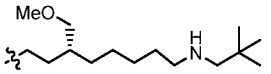
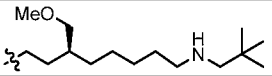
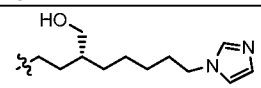
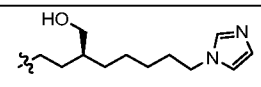
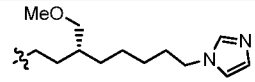
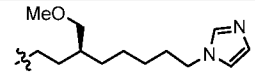
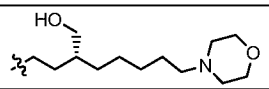
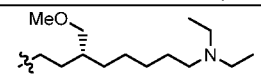
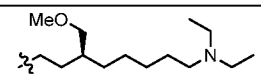
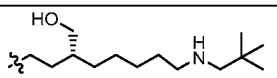
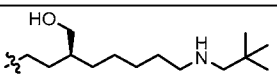
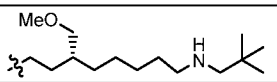
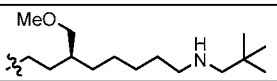
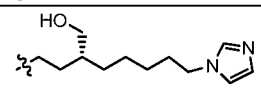
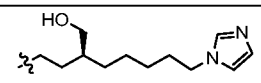
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1115	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1116	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1117	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1118	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1119	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1120	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1121	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1122	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1123	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1125	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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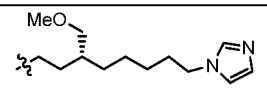
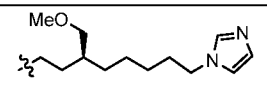
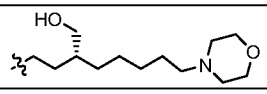
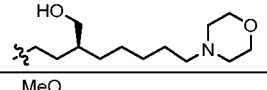
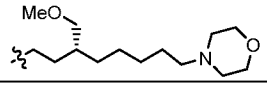
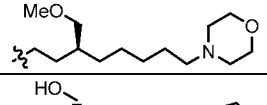
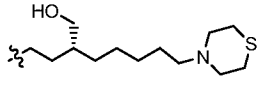
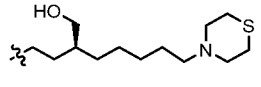
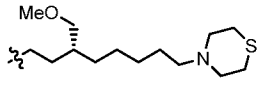
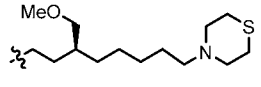
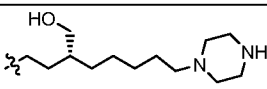
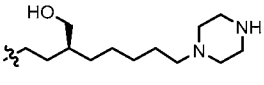
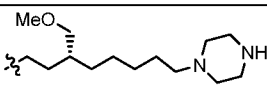
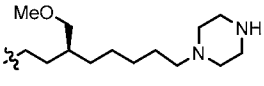
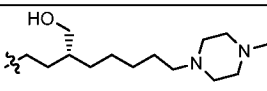
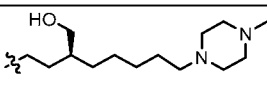
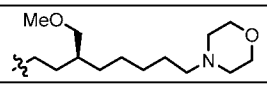
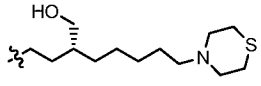
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1128	S		[(S)-(((R)-2-(2-Methoxyethyl)-6-(4-ethylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1129	S		[(S)-(((S)-2-(2-Methoxyethyl)-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1130	S		[(S)-(8-Carboxyoctylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1131	S		[(S)-(8-Carboxyoctylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-potassium salt
1132	S		[(S)-(8-(Ethoxycarbonyl)octylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1133	S		[(S)-((7-Hydroxy-7-methyloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1134	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1135	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin- disodium salt
1136	S		[(S)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1137	S		[(S)-((8-Hydroxy-7-hydroxymethyloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1138	S		[(S)-(((S)-4-Hydroxydecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1139	S		[(S)-(((R)-4-Hydroxydecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1143	S		[(S)-(((R)-4-Hydroxy-10-methylundecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1145	S		[(S)-(((R)-4-Methoxy-10-methylundecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1146	S		[(S)-(((S)-4,9-Dihydroxynonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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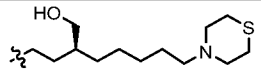
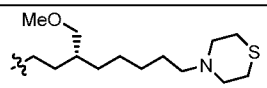
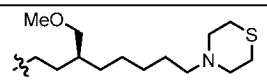
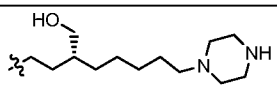
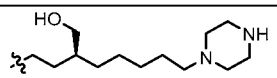
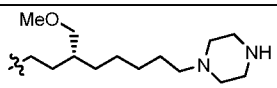
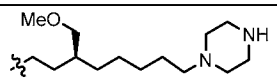
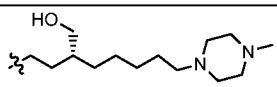
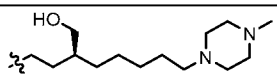
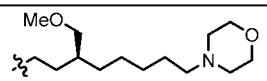
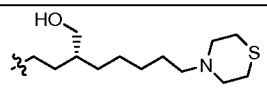
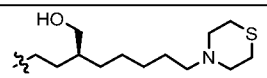
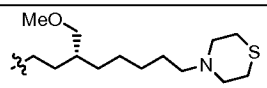
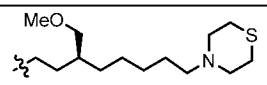
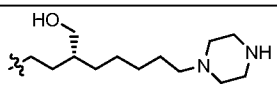
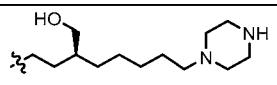
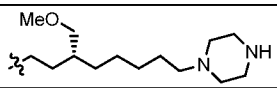
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1149	S		[(S)-(((R)-4-Methoxy-9-hydroxynonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1150	S		[(S)-(((S)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1151	S		[(S)-(((R)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1152	S		[(S)-(((S)-4-Methoxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1153	S		[(S)-(((R)-4-Methoxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1154	S		[(S)-(((S)-4-Hydroxy-9-(dimethylamino)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1162	S		[(S)-(((S)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1163	S		[(S)-(((R)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1164	S		[(S)-(((S)-4-Methoxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1165	S		[(S)-(((R)-4-Methoxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1166	S		[(S)-(((S)-4-Hydroxy-9-(imidazol-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1170	S		[(S)-(((S)-4-Hydroxy-9-morpholinononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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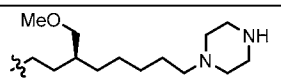
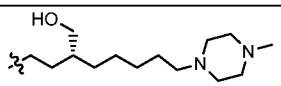
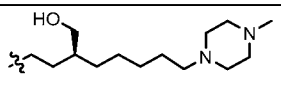
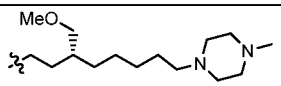
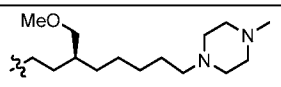
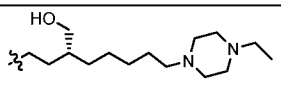
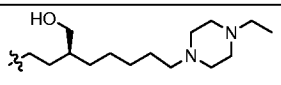
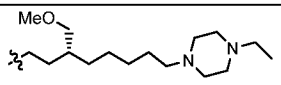
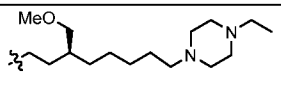
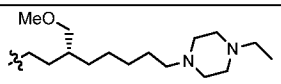
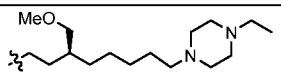
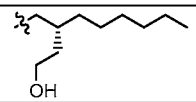
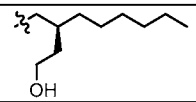
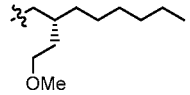
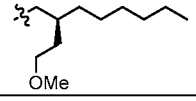
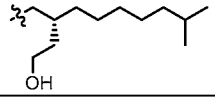
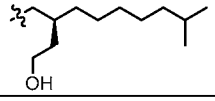
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1173	S		[(S)-(((R)-4-Methoxy-9-morpholinononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1174	S		[(S)-(((S)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1175	S		[(S)-(((R)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1177	S		[(S)-(((R)-4-Methoxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1178	S		[(S)-(((S)-4-Hydroxy-9-piperazin-1-ylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1190	S		[(S)-(((R)-3-(Hydroxymethyl)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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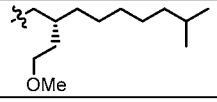
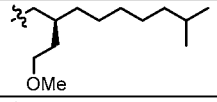
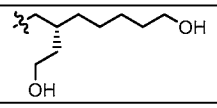
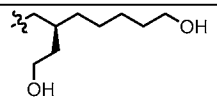
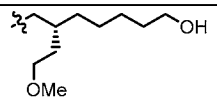
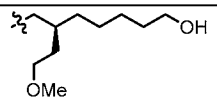
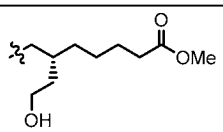
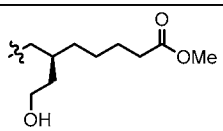
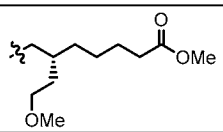
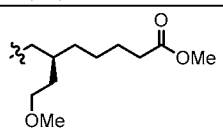
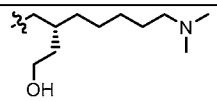
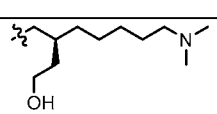
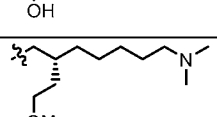
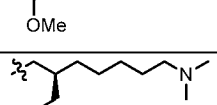
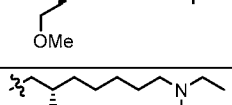
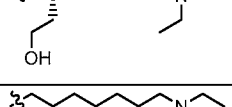
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1193	S		[(S)-(((S)-3-(Methoxymethyl)nonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1194	S		[(S)-(((R)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1195	S		[(S)-(((S)-3-(Methoxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-cyclosporin
1196	S		[(S)-(((R)-3-(Methoxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1197	S		[(S)-(((S)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-cyclosporin
1198	S		[(S)-(((R)-3-(Hydroxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1199	S		[(S)-(((S)-3-(Hydroxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1200	S		[(S)-(((R)-3-(Methoxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1201	S		[(S)-(((S)-3-(Methoxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1202	S		[(S)-(((R)-3-Hydroxymethyl-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1203	S		[(S)-(((S)-3-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1204	S		[(S)-(((R)-3-Methoxymethyl-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1205	S		[(S)-(((S)-3-Methoxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1206	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1207	S		[(S)-(((R)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1208	S		[(S)-(((S)-3-(Methoxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1209	S		[(S)-(((R)-3-(Methoxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1210	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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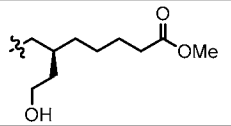
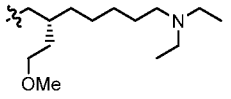
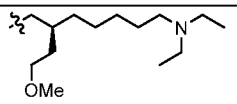
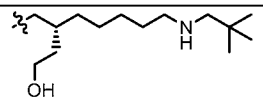
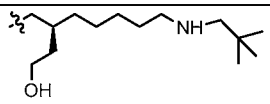
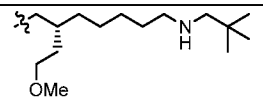
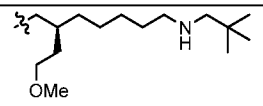
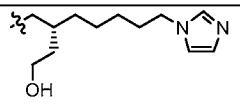
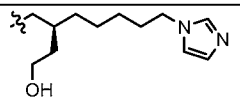
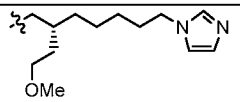
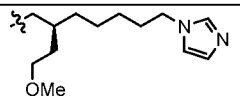
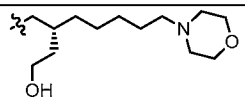
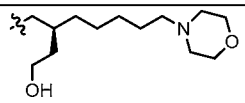
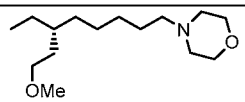
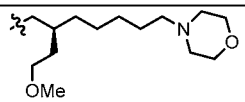
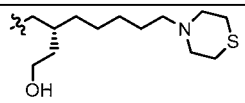
			MeLeu]-4-cyclosporin
1212	S		[(S)-(((S)-3-(Methoxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1213	S		[(S)-(((R)-3-(Methoxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1214	S		[(S)-(((R)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1215	S		[(S)-(((S)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1216	S		[(S)-(((R)-3-Methoxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1217	S		[(S)-(((S)-3-Methoxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1218	S		[(S)-(((R)-3-Hydroxymethyl-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1219	S		[(S)-(((S)-3-Hydroxymethyl-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1220	S		[(S)-(((R)-3-Methoxymethyl-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1221	S		[(S)-(((S)-3-Methoxymethyl-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1222	S		[(S)-(((R)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1223	S		[(S)-(((S)-3-(Methoxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1224	S		[(S)-(((R)-3-(Methoxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1225	S		[(S)-(((R)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1226	S		[(S)-(((S)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1227	S		[(S)-(((R)-3-Methoxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1228	S		[(S)-(((S)-3-Methoxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1229	S		[(S)-(((R)-3-Hydroxymethyl-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1230	S		[(S)-(((S)-3-Hydroxymethyl-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

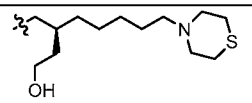
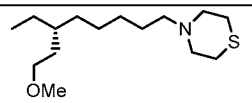
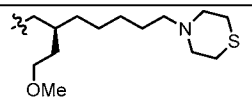
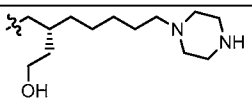
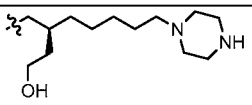
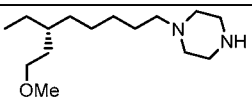
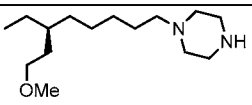
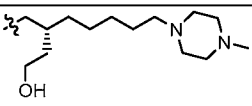
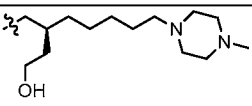
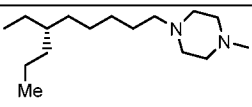
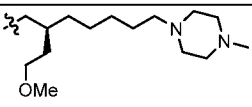
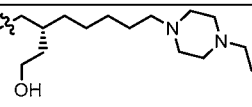
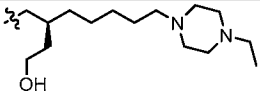
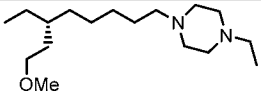
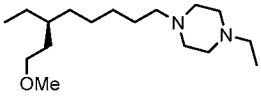
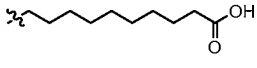
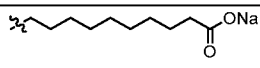
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1232	S		[(S)-(((S)-3-Methoxymethyl-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1233	S		[(S)-(((R)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1234	S		[(S)-(((S)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1235	S		[(S)-(((R)-3-Methoxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1239	S		[(S)-(((R)-3-Methoxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1240	S		[(S)-(((S)-3-Methoxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1241	S		[(S)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1242	S		[(S)-(((S)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1243	S		[(S)-(((R)-3-Methoxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1244	S		[(S)-(((S)-3-Methoxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1245	S		[(S)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1246	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1247	S		[(S)-(((S)-3-Methoxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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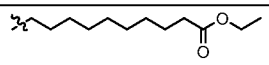
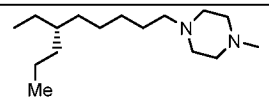
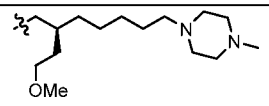
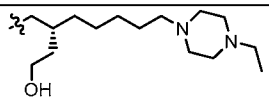
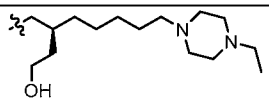
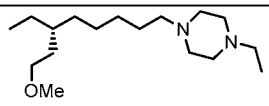
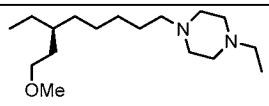
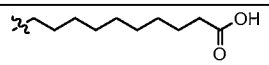
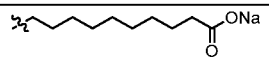
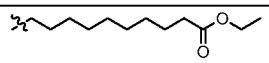
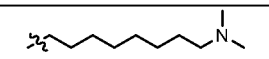
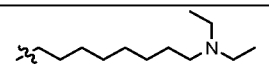
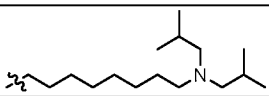
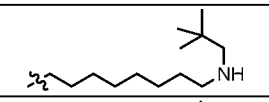
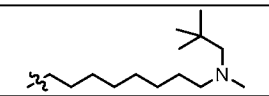
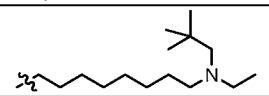
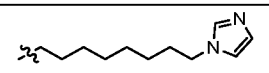
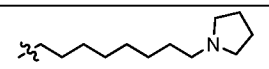
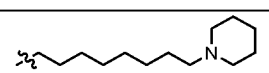
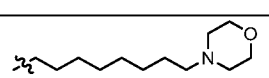
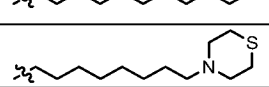
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1251	S		[(S)-(((S)-3-Methoxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1252	S		[(S)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1254	S		[(S)-(((R)-3-Methoxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1255	S		[(S)-(((S)-3-Methoxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1256	S		[(S)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1257	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1258	S		[(S)-(((S)-3-Methoxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1261	S		[(S)-(((R)-3-Methoxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1264	S		[(S)-(((S)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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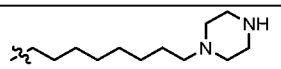
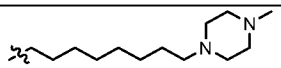
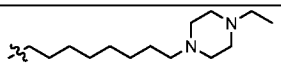
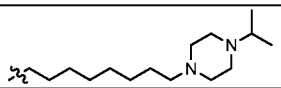
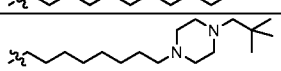
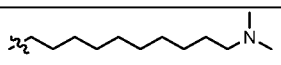
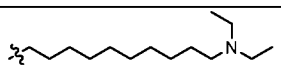
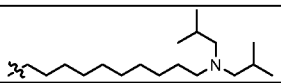
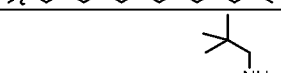
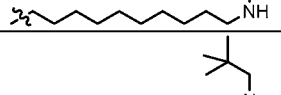
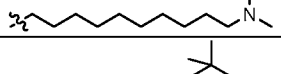
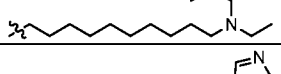
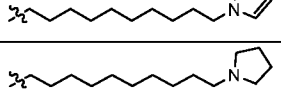
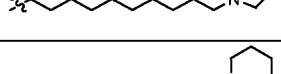
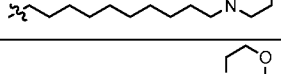
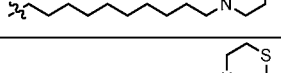
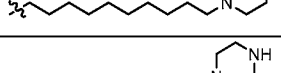
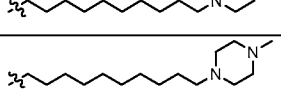
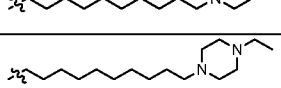
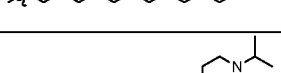
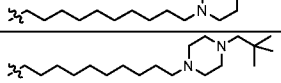
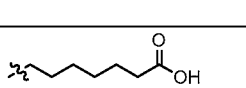
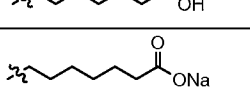
			cyclosporin
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1267	S		[(S)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1268	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1269	S		[(S)-(((R)-3-Methoxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1270	S		[(S)-(((S)-3-Methoxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1271	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1272	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-isopropylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1273	S		[(S)-(((R)-3-Methoxymethyl-6-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1274	S		[(S)-(((S)-3-Methoxymethyl-8-(4-isopropylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1275	S		[(S)-(((R)-3-Methoxymethyl-6-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1276	S		[(S)-(((S)-3-Methoxymethyl-8-(4-isopropylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1277	S		[(S)-(((R)-2-(2-Hydroxyethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1278	S		[(S)-(((S)-2-(2-Hydroxyethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1279	S		[(S)-(((R)-2-(2-Methoxyethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1280	S		[(S)-(((S)-2-(2-Methoxyethyl)octyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1281	S		[(S)-(((R)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1282	S		[(S)-(((S)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

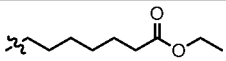
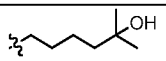
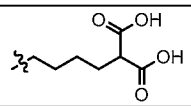
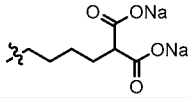
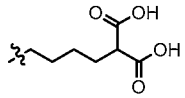
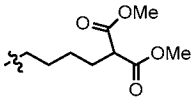
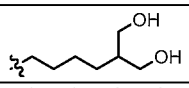
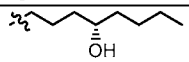
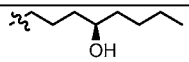
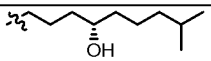
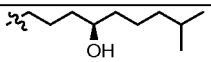
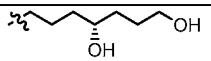
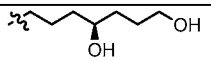
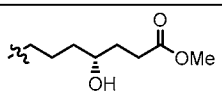
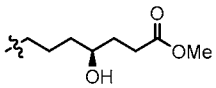
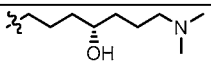
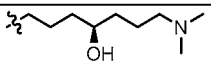
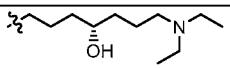
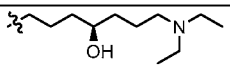
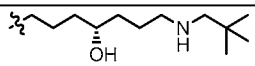
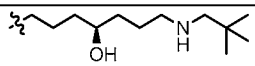
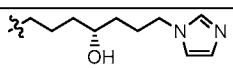
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1284	S		[(S)-(((S)-2-(2-Methoxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1285	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1286	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1287	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1288	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1289	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1290	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1291	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1292	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1293	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1294	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1295	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1296	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1297	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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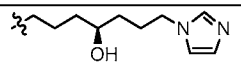
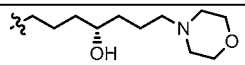
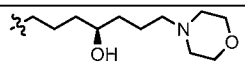
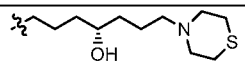
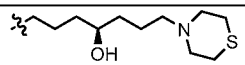
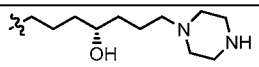
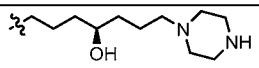
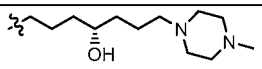
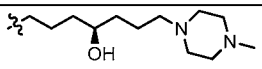
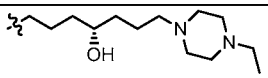
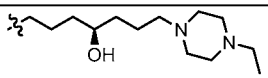
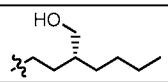
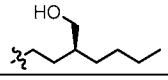
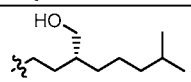
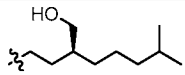
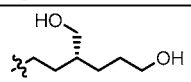
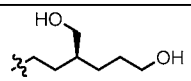
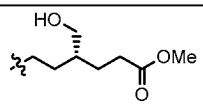
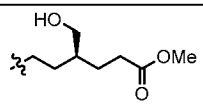
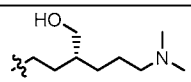
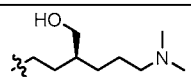
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1300	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1301	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1302	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1303	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1304	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1305	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1306	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1307	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1308	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1309	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1310	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1311	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1312	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1313	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1314	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

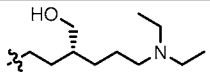
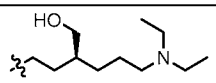
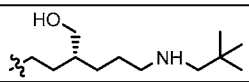
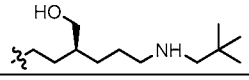
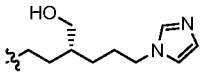
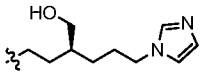
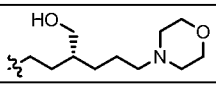
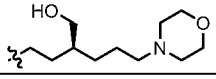
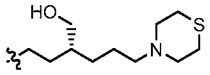
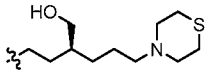
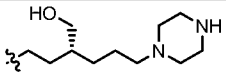
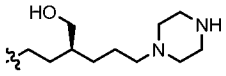
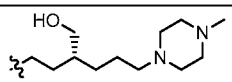
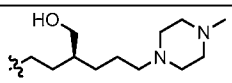
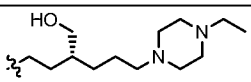
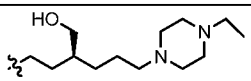
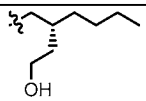
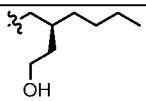
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1316	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1317	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1318	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1319	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1320	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1321	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1322	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1323	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1324	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1325	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1326	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1327	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1328	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1329	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1330	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1331	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-potassium salt

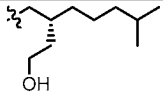
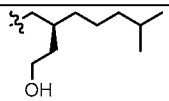
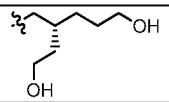
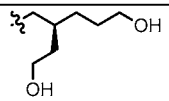
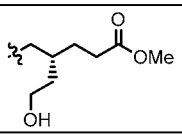
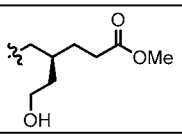
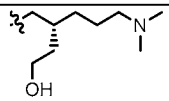
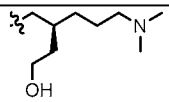
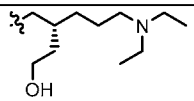
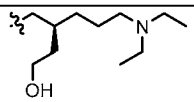
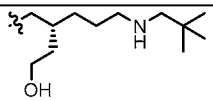
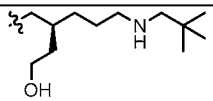
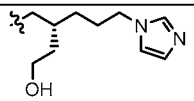
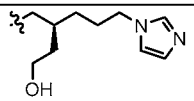
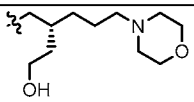
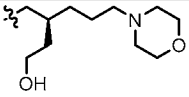
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1333	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1334	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1335	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1336	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1337	S		[(S)-(((R)-2-(2-Methoxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1338	S		[(S)-(((S)-2-(2-Methoxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1339	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1340	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-potassium salt
1341	S		[(S)-(9-(Ethoxycarbonyl)nonylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1342	O		[(R)-(8-(N,N-Dimethylamino)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1343	O		[(R)-(8-(N,N-Diethylamino)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1344	O		[(R)-(8-(N,N-Diisobutylamino)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1345	O		[(R)-(8-(Neopentylamino)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1346	O		[(R)-(8-(N-Methyl-N-neopentyl)amino)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1347	O		[(R)-(8-(N-Ethyl-N-neopentyl)amino)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1348	O		[(R)-(8-(1H-imidazol-1-yl)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1349	O		[(R)-(8-(Pyrrolidin-1-yl)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1350	O		[(R)-(8-(Piperidin-1-yl)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1351	O		[(R)-((8-Morpholinooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1352	O		[(R)-((8-Thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-

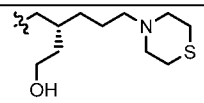
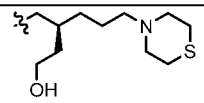
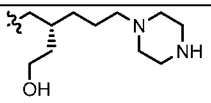
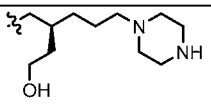
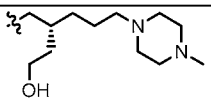
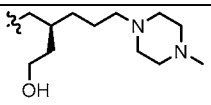
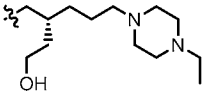
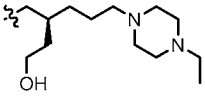
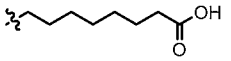
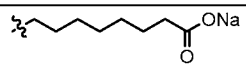
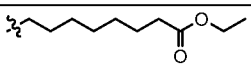
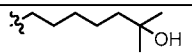
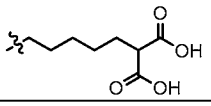
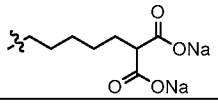
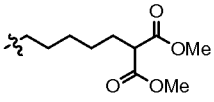
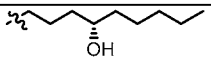
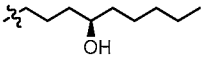
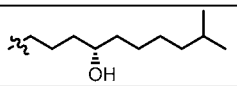
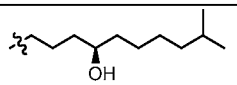
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1353	O		[(R)-((8-(Piperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1354	O		[(R)-((8-(4-Methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1355	O		[(R)-((8-(4-Ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1356	O		[(R)-((8-(4-Isopropylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1357	O		[(R)-((8-(4-Neopentylpiperazin-1-yl)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1358	O		[(R)-(10-(N,N-Dimethylamino)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1359	O		[(R)-(10-(N,N-Diethylamino)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1360	O		[(R)-(10-(N,N-Diisobutylamino)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1361	O		[(R)-(10-(Neopentylamino)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1362	O		[(R)-(10-(N-Methyl-N-neopentyl)amino)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1363	O		[(R)-(10-(N-Ethyl-N-neopentyl)amino)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1364	O		[(R)-(10-(1H-imidazol-1-yl)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1365	O		[(R)-(10-(Pyrrolidin-1-yl)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1366	O		[(R)-(10-(Piperidin-1-yl)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1367	O		[(R)-((10-Morpholinodecyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1368	O		[(R)-((10-Thiomorpholinodecyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1369	O		[(R)-((10-(piperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1370	O		[(R)-((10-(4-methylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1371	O		[(R)-((10-(4-Ethylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1372	O		[(R)-((10-(4-Isopropylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1373	O		[(R)-((10-(4-Neopentylpiperazin-1-yl)decyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1374	O		[(R)-(6-Carboxyhexyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1375	O		[(R)-(6-Carboxyhexyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-sodium salt

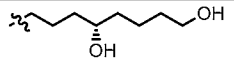
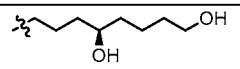
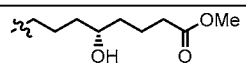
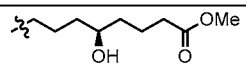
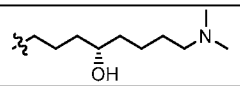
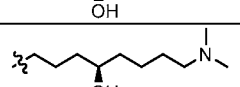
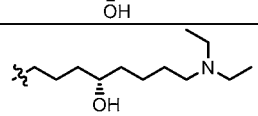
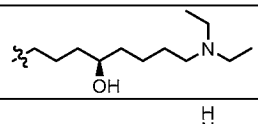
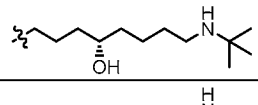
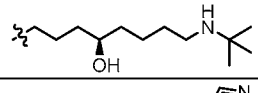
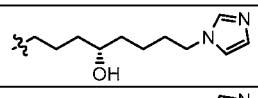
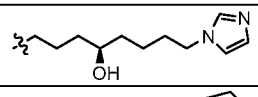
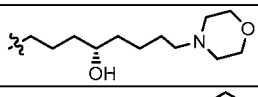
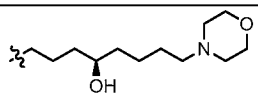
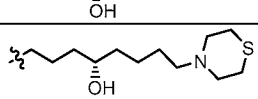
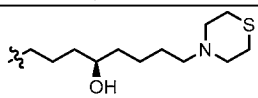
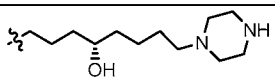
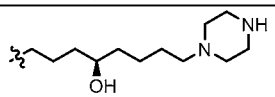
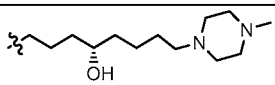
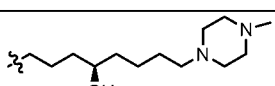
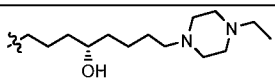
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1377	O		[(R)-((5-Hydroxy-5-methylhexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1378	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1379	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin- disodium salt
1380	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1381	O		[(R)-((6-Methoxy-5-(methoxycarbonyl)-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1382	O		[(R)-((6-Hydroxy-5-hydroxymethylhexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1383	O		[(R)-(((S)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1384	O		[(R)-((R)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1385	O		[(R)-((S)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1386	O		[(R)-((R)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1387	O		[(R)-((S)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1388	O		[(R)-((R)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1389	O		[(R)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1390	O		[(R)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1391	O		[(R)-(((S)-4-Hydroxy-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1392	O		[(R)-(((R)-4-Hydroxy-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1393	O		[(R)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1394	O		[(R)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1395	O		[(R)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1396	O		[(R)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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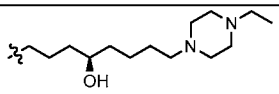
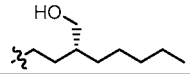
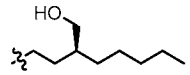
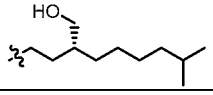
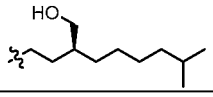
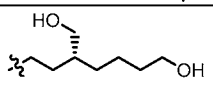
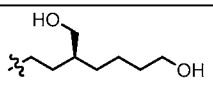
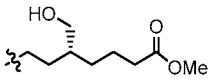
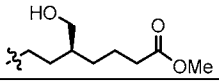
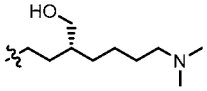
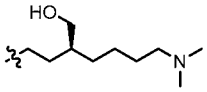
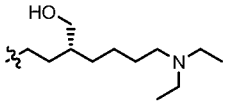
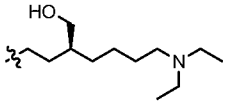
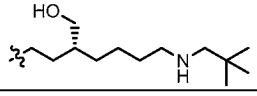
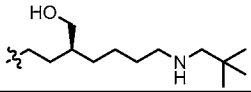
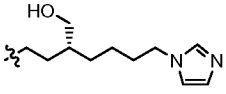
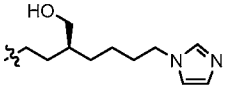
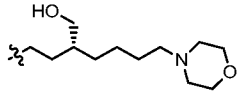
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1400	O		[(R)-(((R)-4-Hydroxy-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1401	O		[(R)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1402	O		[(R)-(((R)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1403	O		[(R)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1404	O		[(R)-(((R)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1405	O		[(R)-(((S)-4-Hydroxy-7-(4-methylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1406	O		[(R)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl)heptyl) oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1407	O		[(R)-(((S)-4-Hydroxy-7-(4-ethylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1408	O		[(R)-(((R)-4-Hydroxy-7-(4-ethylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1409	O		[(R)-(((R)-3-(Hydroxymethyl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1410	O		[(R)-(((S)-3-(Hydroxymethyl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1411	O		[(R)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1415	O		[(R)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1416	O		[(R)-(((S)-3-Hydroxy-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1417	O		[(R)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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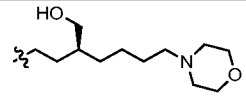
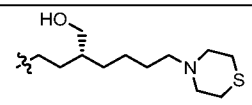
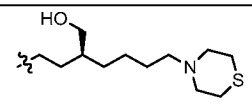
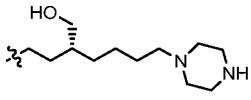
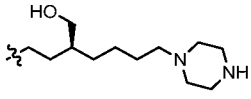
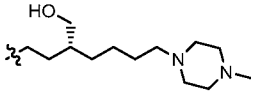
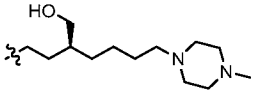
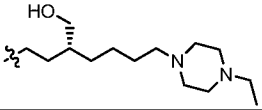
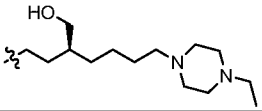
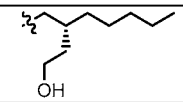
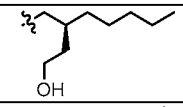
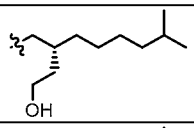
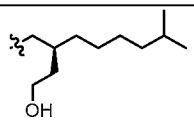
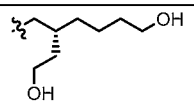
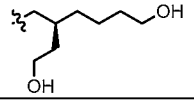
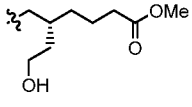
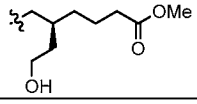
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1420	O		[(R)-(((S)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1421	O		[(R)-(((R)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1422	O		[(R)-(((S)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1423	O		[(R)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1424	O		[(R)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1425	O		[(R)-(((R)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1426	O		[(R)-(((S)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1428	O		[(R)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1429	O		[(R)-(((R)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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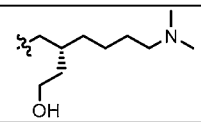
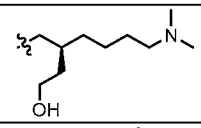
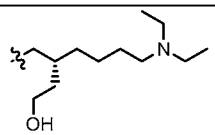
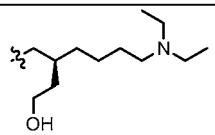
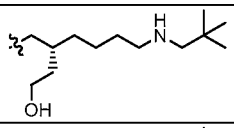
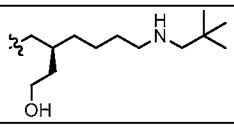
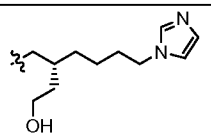
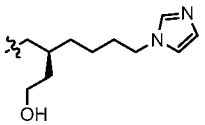
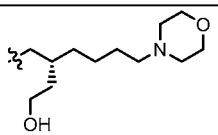
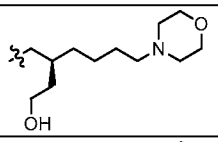
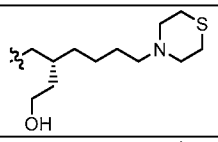
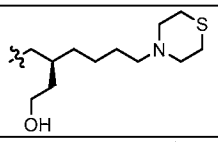
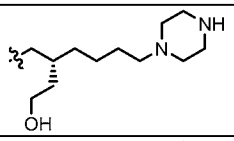
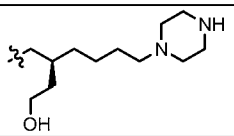
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1438	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1439	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1440	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1441	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1442	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1443	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1444	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1445	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1446	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1447	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1448	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1449	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1450	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1451	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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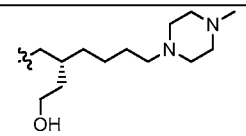
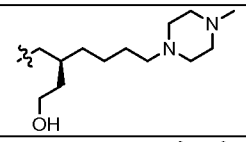
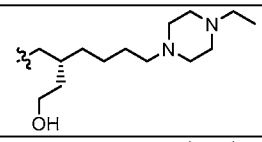
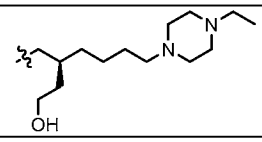
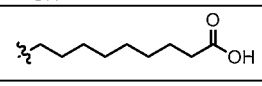
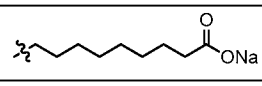
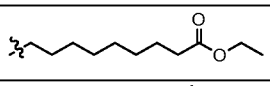
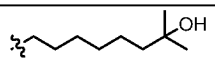
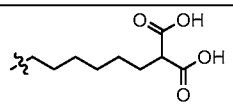
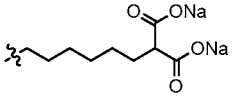
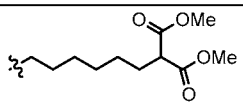
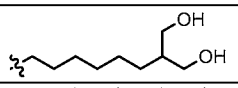
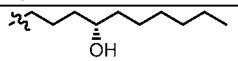
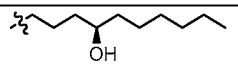
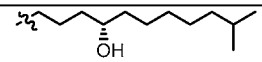
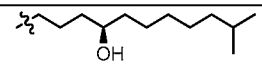
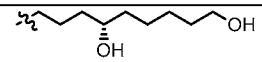
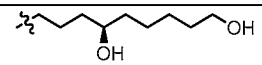
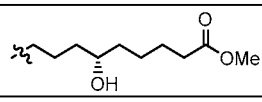
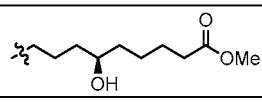
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1454	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1455	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1456	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1457	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1458	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1459	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1460	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1461	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1462	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-sodium salt
1463	O		[(R)-(7-(Ethoxycarbonyl)heptyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1464	O		[(R)-((6-Hydroxy-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1465	O		[(R)-((6,6'-Dicarboxy)hexyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1466	O		[(R)-((6,6'-Dicarboxy)hexyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin- disodium salt
1467	O		[(R)-((7-Methoxy-6-(methoxycarbonyl)-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1468	O		[(R)-((S)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1469	O		[(R)-((R)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1470	O		[(R)-((S)-4-Hydroxy-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1471	O		[(R)-((R)-4-Hydroxy-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

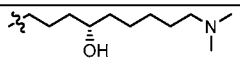
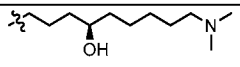
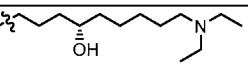
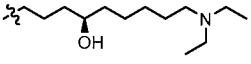
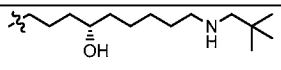
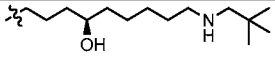
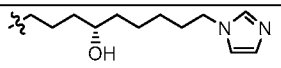
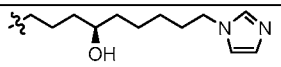
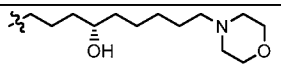
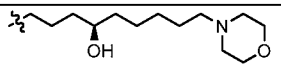
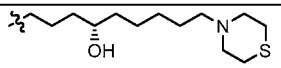
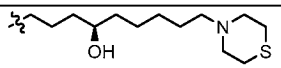
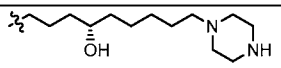
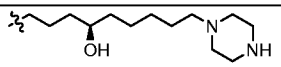
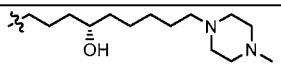
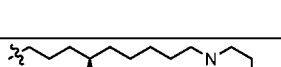
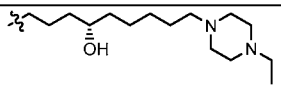
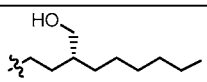
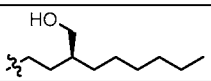
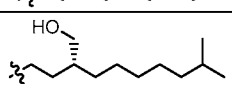
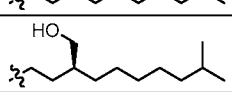
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1473	O		[(R)-(((R)-4,8-Dihydroxyoctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1474	O		[(R)-(((S)-4-Hydroxy-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1475	O		[(R)-(((R)-4-Hydroxy-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1476	O		[(R)-(((S)-4-Hydroxy-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1477	O		[(R)-(((R)-4-Hydroxy-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1478	O		[(R)-(((S)-4-Hydroxy-8-(diethylamino)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1479	O		[(R)-(((R)-4-Hydroxy-8-(diethylamino)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1480	O		[(R)-(((S)-4-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1481	O		[(R)-(((R)-4-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1482	O		[(R)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1483	O		[(R)-(((R)-4-Hydroxy-8-(imidazo-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1484	O		[(R)-(((S)-4-Hydroxy-8-morpholinooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1485	O		[(R)-(((R)-4-Hydroxy-8-morpholinooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1486	O		[(R)-(((S)-4-Hydroxy-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1487	O		[(R)-(((R)-4-Hydroxy-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1488	O		[(R)-(((S)-4-Hydroxy-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1489	O		[(R)-(((R)-4-Hydroxy-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1490	O		[(R)-(((S)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1491	O		[(R)-(((R)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1492	O		[(R)-(((S)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

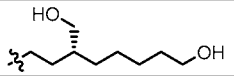
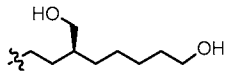
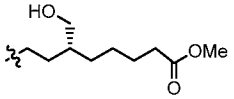
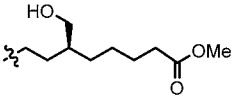
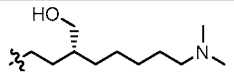
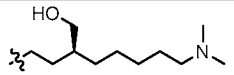
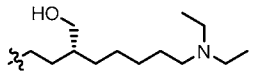
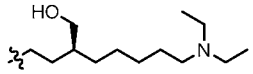
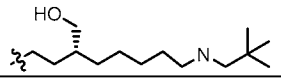
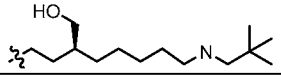
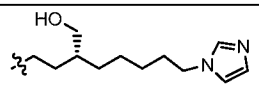
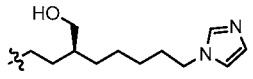
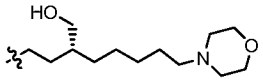
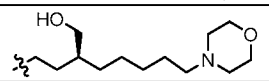
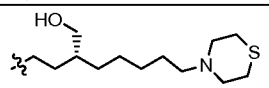
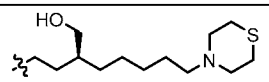
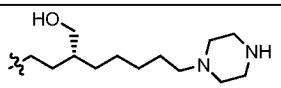
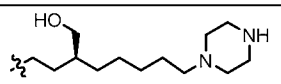
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1494	O		[(R)-(((R)-3-(Hydroxymethyl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1495	O		[(R)-(((S)-3-(Hydroxymethyl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1496	O		[(R)-(((R)-3-(Hydroxymethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1497	O		[(R)-(((S)-3-(Hydroxymethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1498	O		[(R)-((((R)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1499	O		[(R)-((((S)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1500	O		[(R)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1501	O		[(R)-(((S)-3-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1502	O		[(R)-(((R)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1503	O		[(R)-(((S)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1504	O		[(R)-(((R)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1505	O		[(R)-(((S)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1506	O		[(R)-(((R)-3-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1507	O		[(R)-(((S)-3-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1508	O		[(R)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1509	O		[(R)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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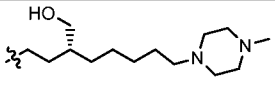
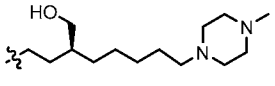
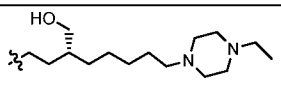
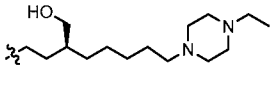
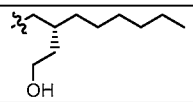
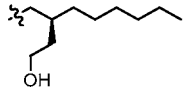
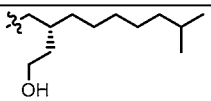
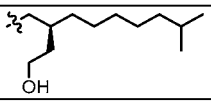
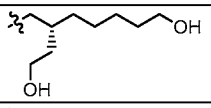
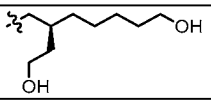
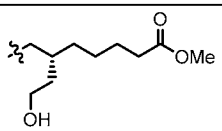
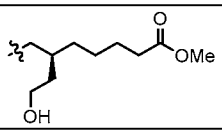
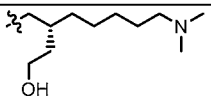
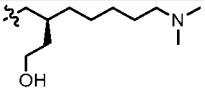
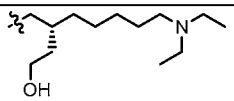
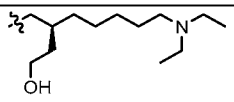
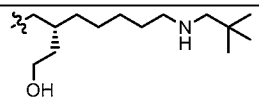
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1513	O		[(R)-(((S)-3-Hydroxymethyl-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1514	O		[(R)-(((R)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1517	O		[(R)-(((S)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1519	O		[(R)-(((S)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1527	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-

			cyclosporin
1528	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1530	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1531	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1532	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1533	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(neopentylamino)hepxyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1534	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(imidazol-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1535	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(imidazo-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1536	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1537	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1538	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1539	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1540	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1541	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

1542	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1543	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1544	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(4-ethylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1545	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(4-isopropylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1546	O		[(R)-(8-Carboxyoctyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1547	O		[(R)-(8-Carboxyoctyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-potassium salt
1548	O		[(R)-(8-(Ethoxycarbonyl)octyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1549	O		[(R)-((7-Hydroxy-7-methyloctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1550	O		[(R)-((7,7'-Dicarboxy)heptyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1551	O		[(R)-((7,7'-Dicarboxy)heptyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin- disodium salt
1552	O		[(R)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1553	O		[(R)-((8-Hydroxy-7-hydroxymethyloctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1554	O		[(R)-(((S)-4-Hydroxydecyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1600	O		[(R)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1601	O		[(R)-(((S)-3-Hydroxymethyl-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

1602	O		[(R)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1603	O		[(R)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1609	O		[(R)-(((S)-2-(2-Hydroxyethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1612	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1614	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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1616	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1617	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
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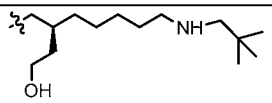
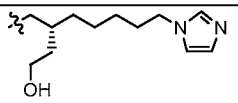
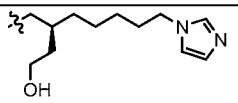
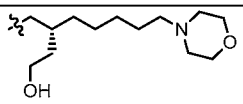
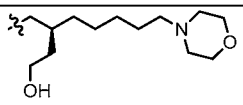
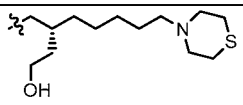
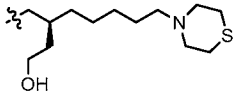
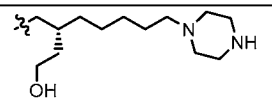
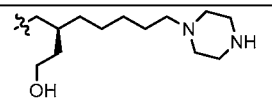
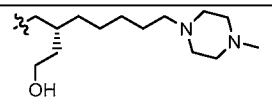
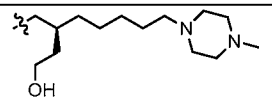
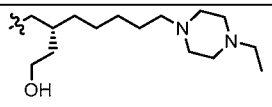
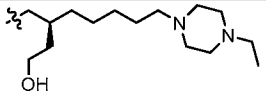
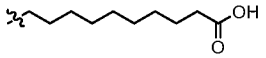
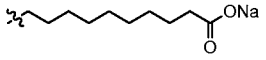
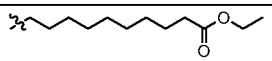
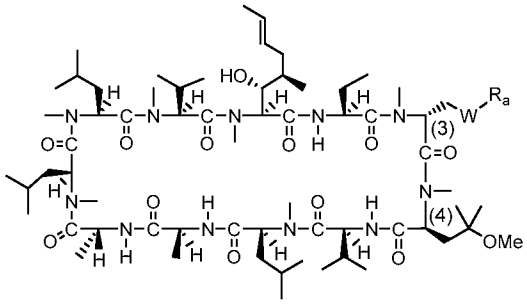
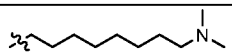
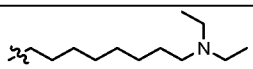
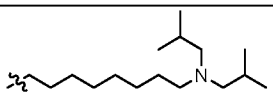
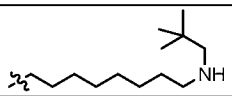
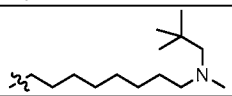
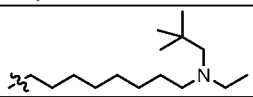
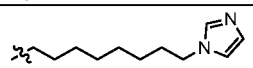
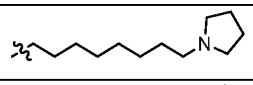
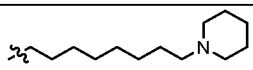
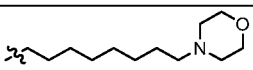
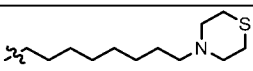
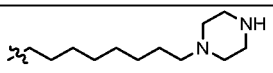
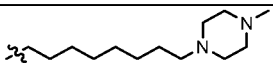
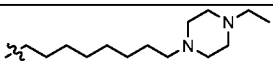
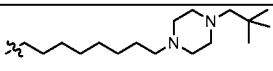
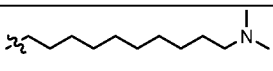
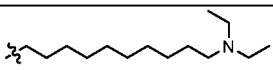
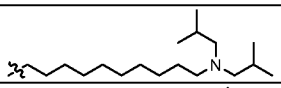
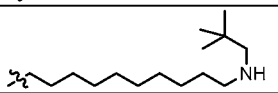
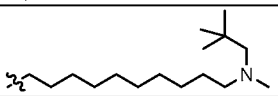
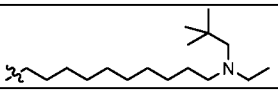
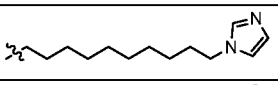
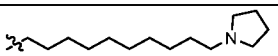
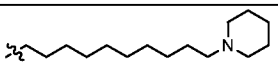
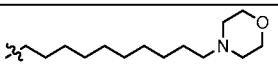
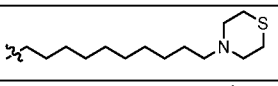
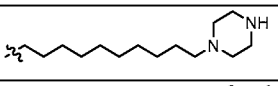
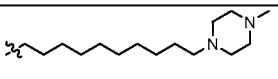
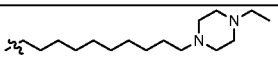
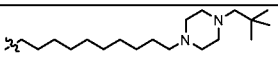
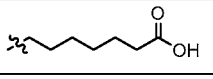
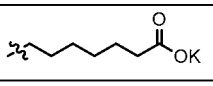
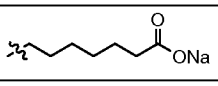
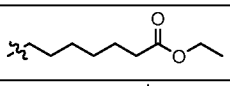
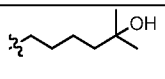
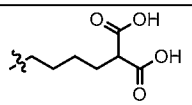
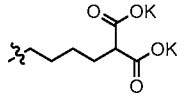
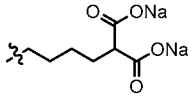
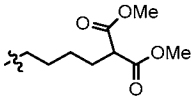
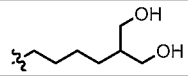
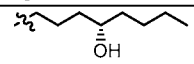
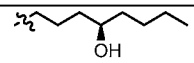
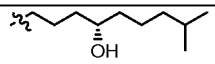
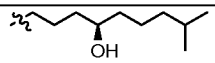
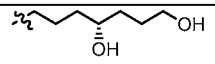
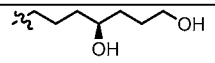
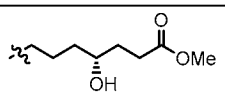
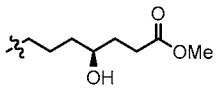
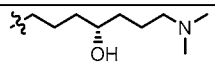
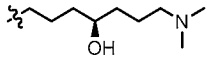
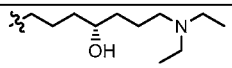
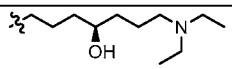
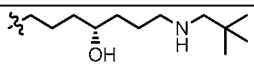
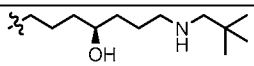
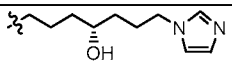
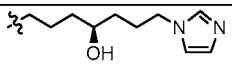
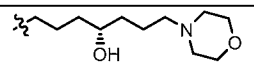
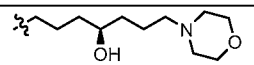
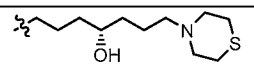
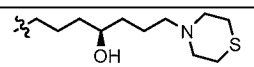
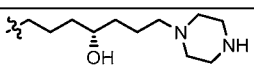
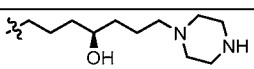
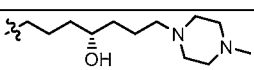
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1622	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1623	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1624	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1625	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1626	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1627	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1628	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1629	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1630	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1631	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1632	O		[(R)-(9-Carboxynonyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin
1633	O		[(R)-(9-Carboxynonyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin-potassium salt
1634	O		[(R)-(9-(Ethoxycarbonyl)nonyloxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin

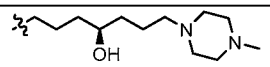
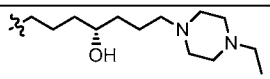
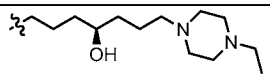
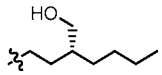
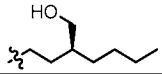
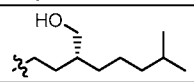
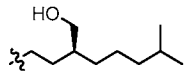
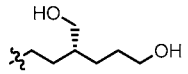
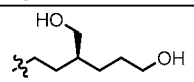
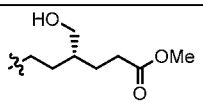
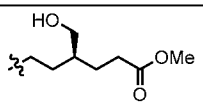
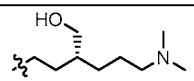
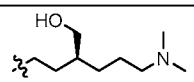
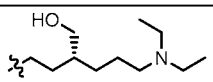
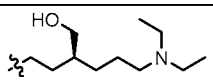
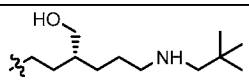
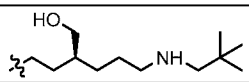
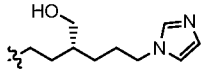
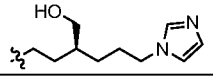
Table 3

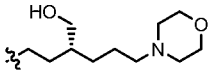
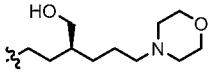
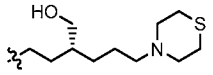
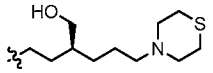
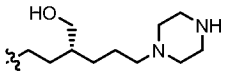
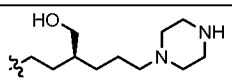
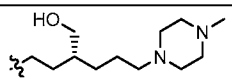
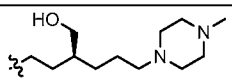
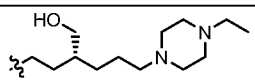
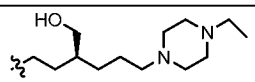
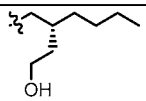
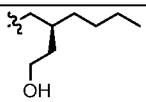
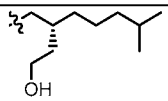
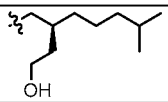
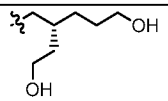
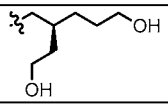
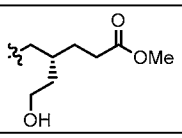


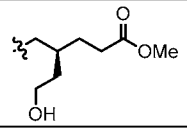
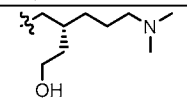
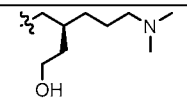
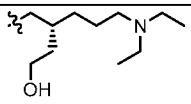
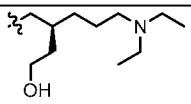
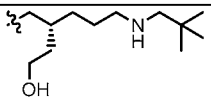
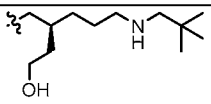
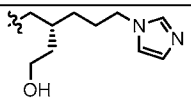
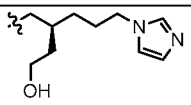
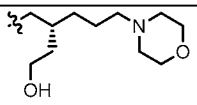
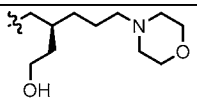
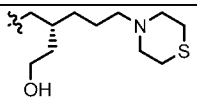
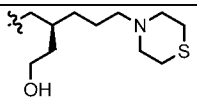
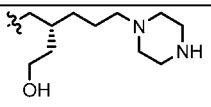
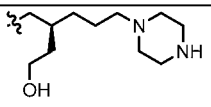
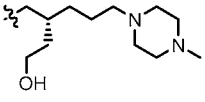
Ex. No.	W	R_a	Name
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1636	S		[(S)-(8-(N,N-Diethylamino)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1637	S		[(S)-(8-(N,N-Diisobutylamino)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1638	S		[(S)-(8-(Neopentylamino)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1639	S		[(S)-(8-(N-Methyl-N-neopentyl)amino)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1640	S		[(S)-(8-(N-Ethyl-N-neopentyl)amino)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1641	S		[(S)-(8-(1H-imidazol-1-yl)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1642	S		[(S)-(8-(Pyrrolidin-1-yl)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1643	S		[(S)-(8-(Piperidin-1-yl)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1644	S		[(S)-((8-Morpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1645	S		[(S)-((8-Thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1646	S		[(S)-((8-(Piperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1647	S		[(S)-((8-(4-Methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1648	S		[(S)-((8-(4-Ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1649	S		[(S)-((8-(4-Neopentylpiperazin-1-yl)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1650	S		[(S)-(10-(N,N-Dimethylamino)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1651	S		[(S)-(10-(N,N-Diethylamino)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

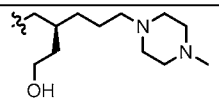
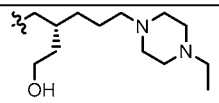
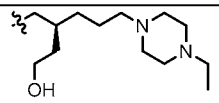
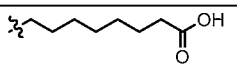
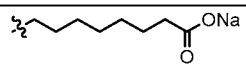
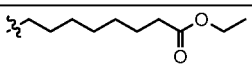
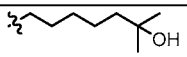
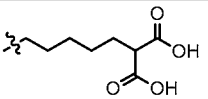
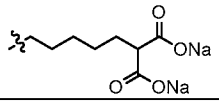
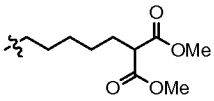
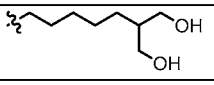
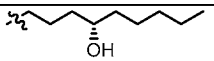
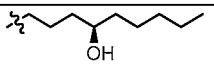
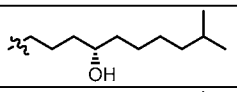
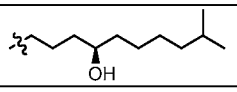
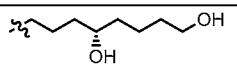
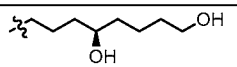
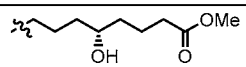
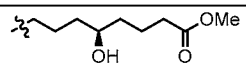
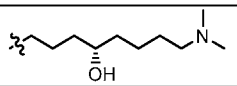
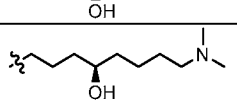
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1653	S		[(S)-(10-(Neopentylamino)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1654	S		[(S)-(10-(methyl(neopentyl)amino)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1655	S		[(S)-(10-(Ethyl(neopentyl)amino)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1656	S		[(S)-(10-(1H-imidazol-1-yl)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1657	S		[(S)-(10-(Pyrrolidin-1-yl)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1658	S		[(S)-(10-(Piperidin-1-yl)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1659	S		[(S)-((10-Morpholinodecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1660	S		[(S)-((10-Thiomorpholinodecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1661	S		[(S)-((10-(Piperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1662	S		[(S)-((10-(4-Methylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1663	S		[(S)-((10-(4-Ethylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1664	S		[(S)-((10-(4-Neopentylpiperazin-1-yl)decylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1665	S		[(S)-(6-Carboxyhexylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1666	S		[(S)-(6-Carboxyhexylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-potassium salt
1667	S		[(S)-(6-Carboxyhexylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-sodium salt
1668	S		[(S)-(6-(Ethoxycarbonyl)hexylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1669	S		[(S)-((5-Hydroxy-5-methylhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1670	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1671	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin- dipotassium salt
1672	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin- disodium salt
1673	S		[(S)-((6-Methoxy-5-(methoxycarbonyl)-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

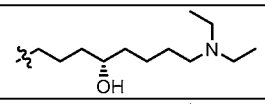
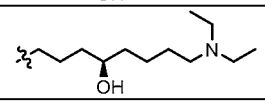
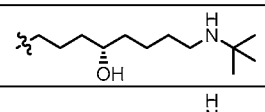
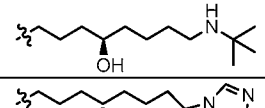
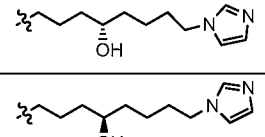
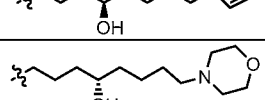
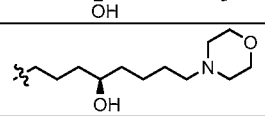
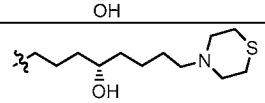
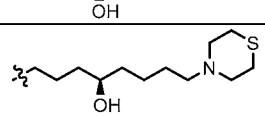
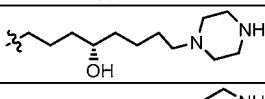
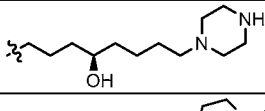
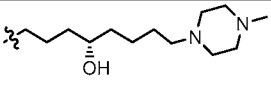
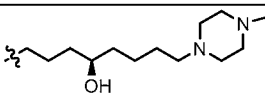
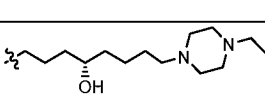
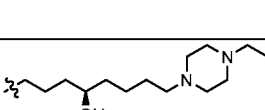
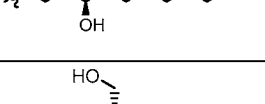
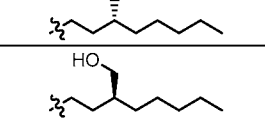
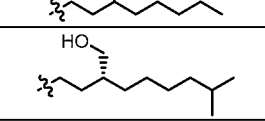
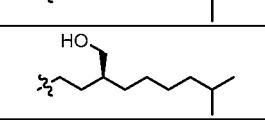
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1675	S		[(S)-((S)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1676	S		[(S)-((R)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1677	S		[(S)-((S)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1678	S		[(S)-((R)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1679	S		[(S)-((S)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1680	S		[(S)-((R)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1681	S		[(S)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1682	S		[(S)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1683	S		[(S)-(((S)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1684	S		[(S)-(((R)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1685	S		[(S)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1686	S		[(S)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1687	S		[(S)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1688	S		[(S)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1689	S		[(S)-(((S)-4-Hydroxy-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1690	S		[(S)-(((R)-4-Hydroxy-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1691	S		[(S)-(((S)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1692	S		[(S)-(((R)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1693	S		[(S)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1694	S		[(S)-(((R)-4-Hydroxy-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1695	S		[(S)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1696	S		[(S)-(((R)-4-Hydroxy-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1697	S		[(S)-(((S)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-

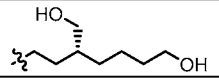
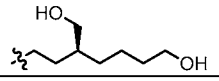
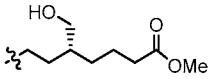
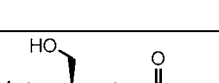
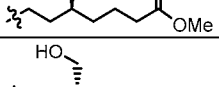
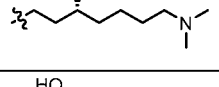
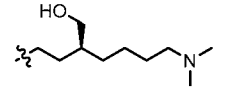
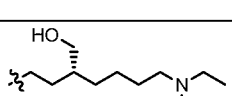
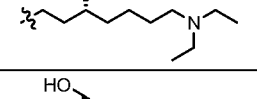
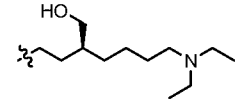
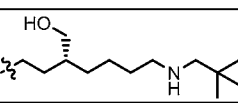
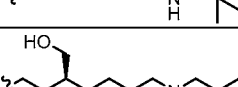
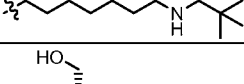
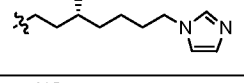
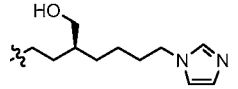
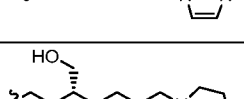
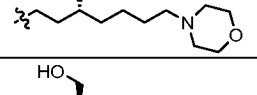
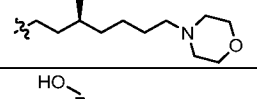
			cyclosporin
1698	S		[(S)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1699	S		[(S)-(((S)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1700	S		[(S)-(((R)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1701	S		[(S)-(((R)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1702	S		[(S)-(((S)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1703	S		[(S)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1704	S		[(S)-(((S)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1705	S		[(S)-(((R)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1706	S		[(S)-(((S)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1707	S		[(S)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1708	S		[(S)-(((S)-3-Hydroxy-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1709	S		[(S)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1710	S		[(S)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1711	S		[(S)-(((R)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1712	S		[(S)-(((S)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1713	S		[(S)-(((R)-3-Hydroxy-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1714	S		[(S)-(((S)-3-Hydroxy-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1715	S		[(S)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1716	S		[(S)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-

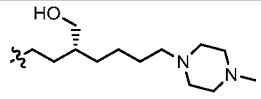
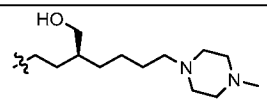
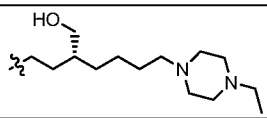
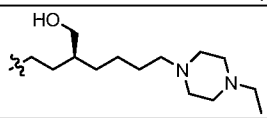
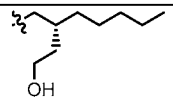
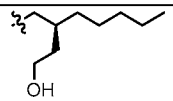
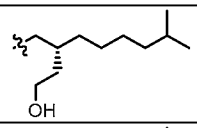
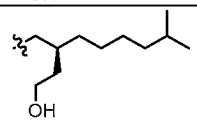
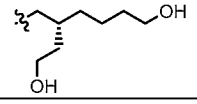
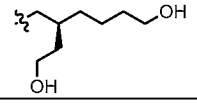
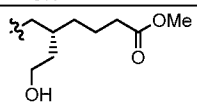
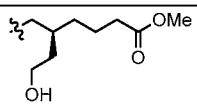
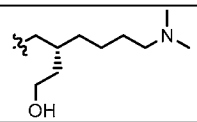
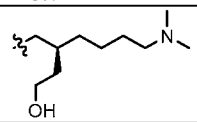
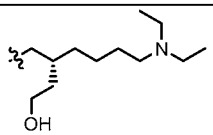
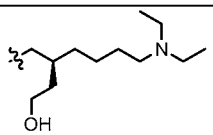
			cyclosporin
1717	S		[(S)-(((R)-3-Hydroxymethyl-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1718	S		[(S)-(((S)-3-Hydroxymethyl-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1719	S		[(S)-(((R)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1720	S		[(S)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1721	S		[(S)-(((R)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1722	S		[(S)-(((S)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1723	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1724	S		[(S)-(((S)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1725	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1726	S		[(S)-(((S)-3-Hydroxymethyl-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1727	S		[(S)-(((R)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1728	S		[(S)-(((S)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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1732	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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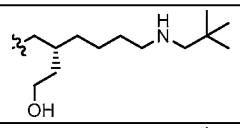
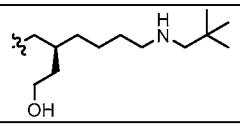
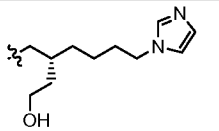
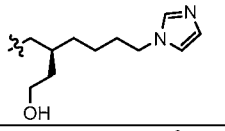
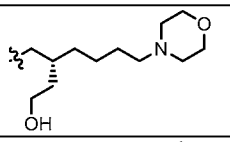
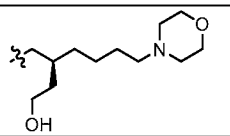
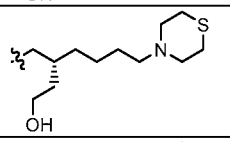
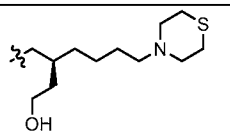
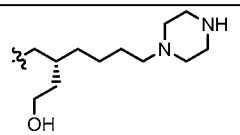
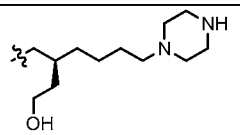
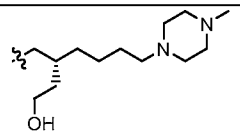
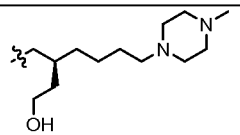
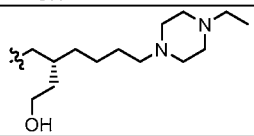
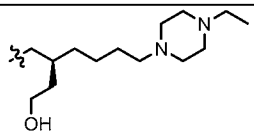
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1735	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1736	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1737	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1738	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1739	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1740	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1741	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1742	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1743	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1744	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1745	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1746	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1747	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1748	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1749	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

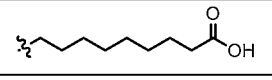
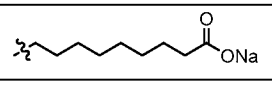
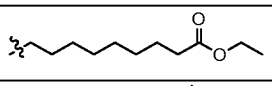
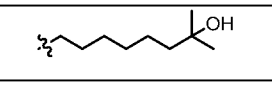
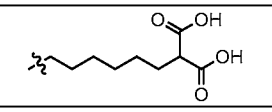
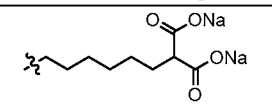
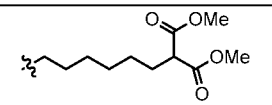
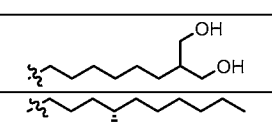
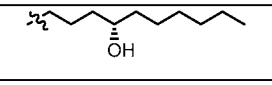
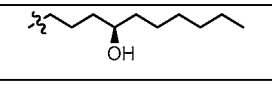
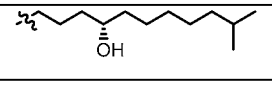
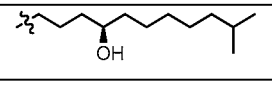
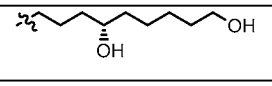
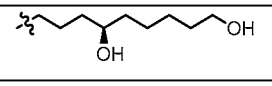
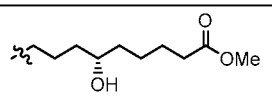
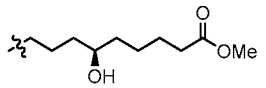
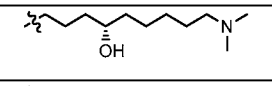
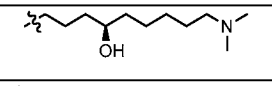
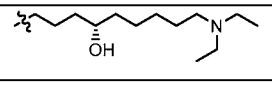
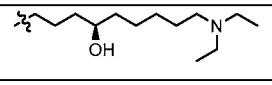
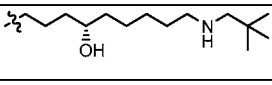
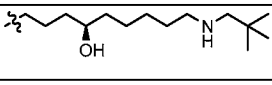
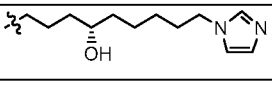
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1751	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1752	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1753	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1754	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-sodium salt
1755	S		[(S)-(7-(Ethoxycarbonyl)heptylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1756	S		[(S)-((6-Hydroxy-6-methylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1757	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1758	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin- disodium salt
1759	S		[(S)-((7-Methoxy-6-(methoxycarbonyl)-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1760	S		[(S)-((7-Hydroxy-6-hydroxymethylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1761	S		[(S)-((S)-(4-Hydroxynonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1762	S		[(S)-((R)-(4-Hydroxynonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1763	S		[(S)-((S)-4-Hydroxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1764	S		[(S)-((R)-4-Hydroxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1765	S		[(S)-(((S)-4,8-Dihydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1766	S		[(S)-(((R)-4,8-Dihydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1767	S		[(S)-(((S)-4-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1768	S		[(S)-(((R)-4-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1769	S		[(S)-(((S)-4-Hydroxy-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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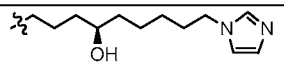
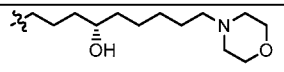
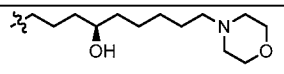
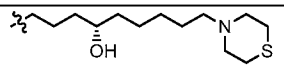
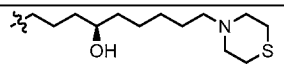
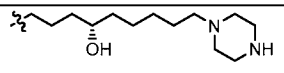
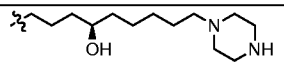
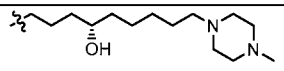
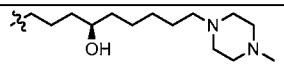
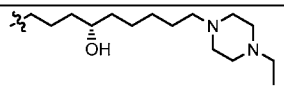
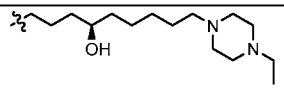
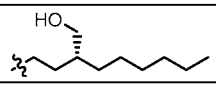
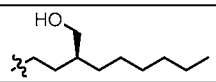
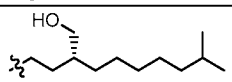
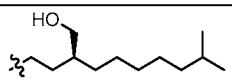
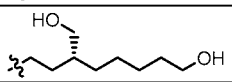
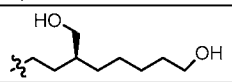
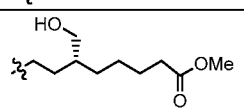
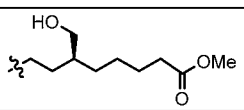
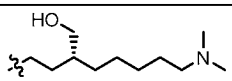
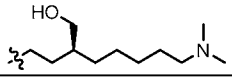
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1772	S		[(S)-(((R)-4-Hydroxy-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1773	S		[(S)-(((S)-4-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1774	S		[(S)-(((R)-4-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1775	S		[(S)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1776	S		[(S)-(((R)-4-Hydroxy-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1777	S		[(S)-(((S)-4-Hydroxy-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1778	S		[(S)-(((R)-4-Hydroxy-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1779	S		[(S)-(((S)-4-Hydroxy-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1780	S		[(S)-(((R)-4-Hydroxy-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1781	S		[(S)-(((S)-4-Hydroxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1782	S		[(S)-(((R)-4-Hydroxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1783	S		[(S)-(((S)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1784	S		[(S)-(((R)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1785	S		[(S)-(((S)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1786	S		[(S)-(((R)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1787	S		[(S)-(((R)-3-(Hydroxymethyl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1788	S		[(S)-(((S)-3-(Hydroxymethyl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1789	S		[(S)-(((R)-3-(Hydroxymethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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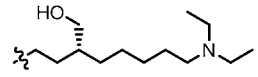
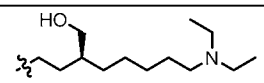
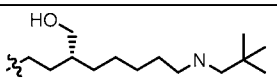
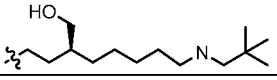
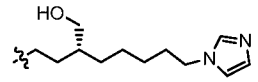
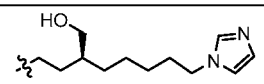
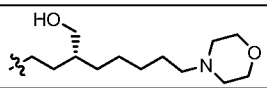
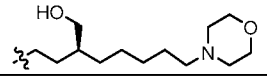
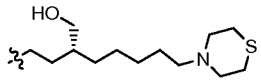
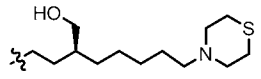
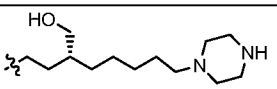
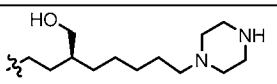
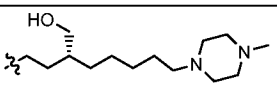
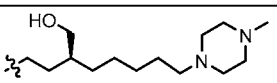
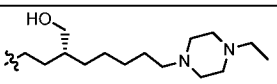
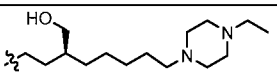
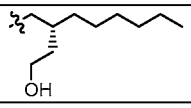
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1792	S		[(S)-((((S)-3-(Hydroxymethyl)-7-hydroxyl)hepyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1793	S		[(S)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1794	S		[(S)-(((S)-3-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1795	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1796	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1797	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1798	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1799	S		[(S)-(((R)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1800	S		[(S)-(((S)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1801	S		[(S)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1802	S		[(S)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1803	S		[(S)-(((R)-3-Hydroxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1804	S		[(S)-(((S)-3-Hydroxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1805	S		[(S)-(((R)-3-Hydroxymethyl-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1806	S		[(S)-(((S)-3-Hydroxymethyl-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1807	S		[(S)-(((R)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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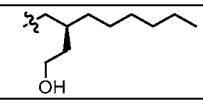
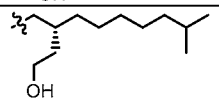
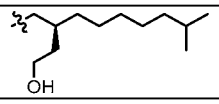
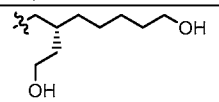
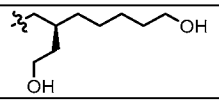
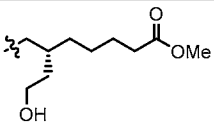
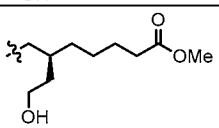
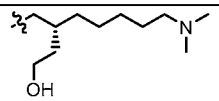
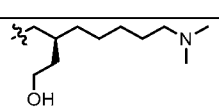
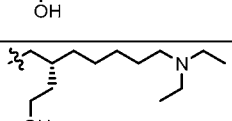
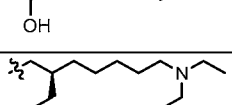
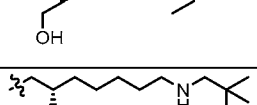
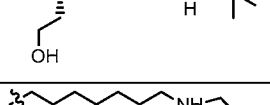
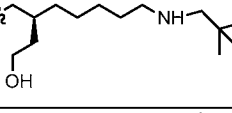
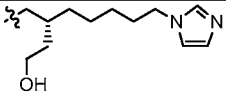
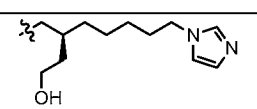
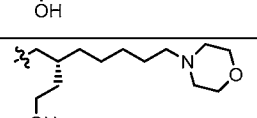
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1810	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1811	S		[(S)-(((R)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1812	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1813	S		[(S)-(((R)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1814	S		[(S)-(((S)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1815	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1816	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1817	S		[(S)-((((R)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-cyclosporin
1818	S		[(S)-((((S)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1819	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1820	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1821	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1822	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1823	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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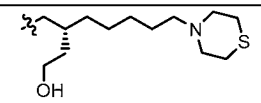
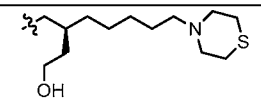
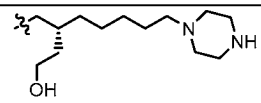
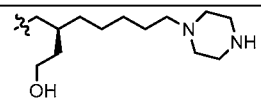
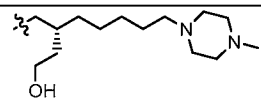
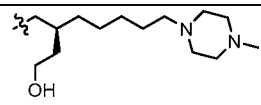
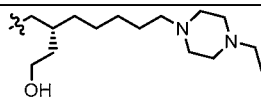
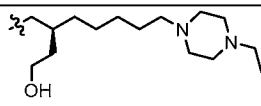
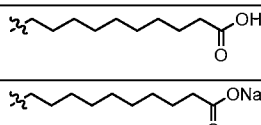
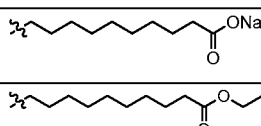
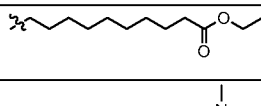
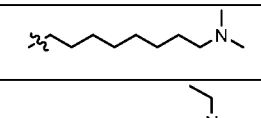
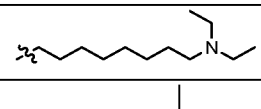
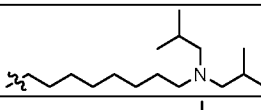
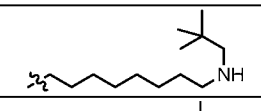
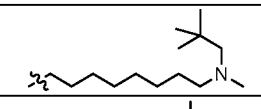
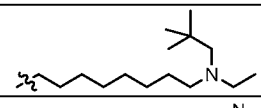
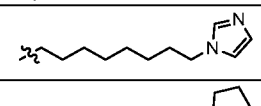
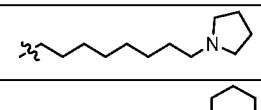
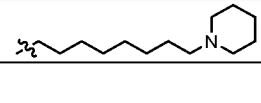
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1826	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(neopentylamino)hepxyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1827	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1828	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1829	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1830	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1831	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1832	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1833	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1834	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1835	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1836	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1837	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(4-ethylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1838	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

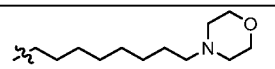
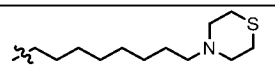
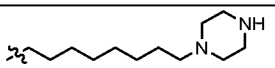
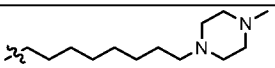
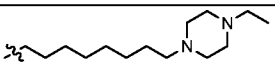
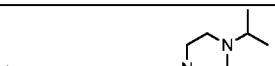
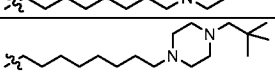
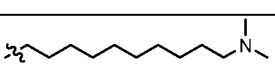
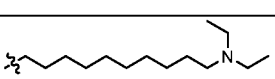
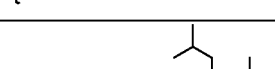
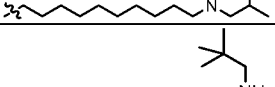
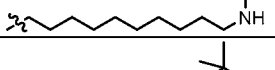
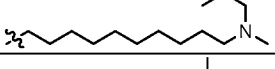
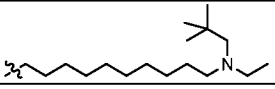
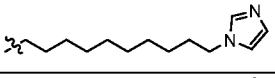
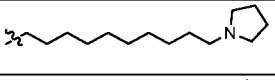
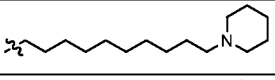
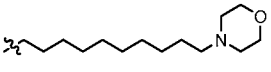
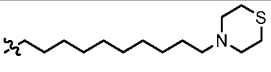
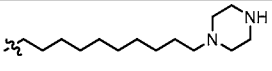
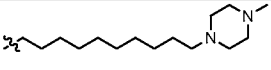
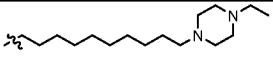
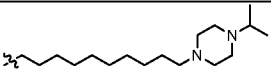
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1840	S		[(S)-(8-Carboxyoctylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-potassium salt
1841	S		[(S)-(8-(Ethoxycarbonyl)octylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1842	S		[(S)-((7-Hydroxy-7-methyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1843	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1844	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin- disodium salt
1845	S		[(S)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1846	S		[(S)-((8-Hydroxy-7-hydroxymethyloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1847	S		[(S)-(((S)-4-Hydroxydecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1848	S		[(S)-(((R)-4-Hydroxydecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1849	S		[(S)-(((S)-4-Hydroxy-10-methylundecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1850	S		[(S)-(((R)-4-Hydroxy-10-methylundecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1851	S		[(S)-(((S)-4,9-Dihydroxynonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1852	S		[(S)-(((R)-4,9-Dihydroxynonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1853	S		[(S)-(((S)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1854	S		[(S)-(((R)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1855	S		[(S)-(((S)-4-Hydroxy-9-(dimethylamino)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1856	S		[(S)-(((R)-4-Hydroxy-9-(dimethylamino)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1857	S		[(S)-(((S)-4-Hydroxy-9-(diethylamino)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1858	S		[(S)-(((R)-4-Hydroxy-9-(diethylamino)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1859	S		[(S)-(((S)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1860	S		[(S)-(((R)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1861	S		[(S)-(((S)-4-Hydroxy-9-(imidazol-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

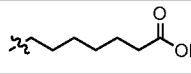
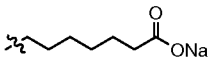
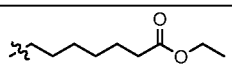
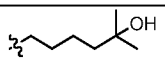
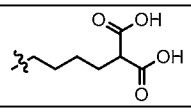
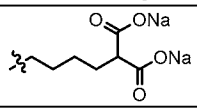
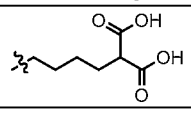
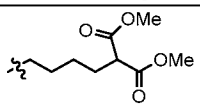
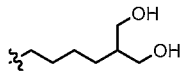
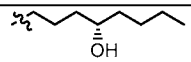
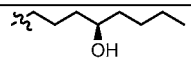
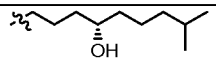
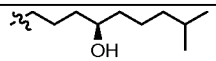
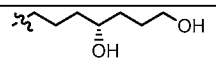
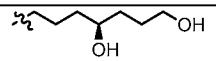
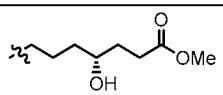
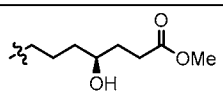
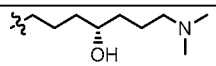
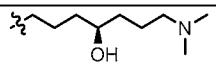
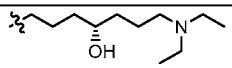
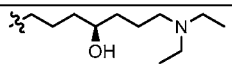
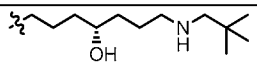
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1863	S		[(S)-(((S)-4-Hydroxy-9-morpholinononyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1864	S		[(S)-(((R)-4-Hydroxy-9-morpholinononyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1865	S		[(S)-(((S)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1866	S		[(S)-(((R)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1867	S		[(S)-(((S)-4-Hydroxy-9-piperazin-1-ylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1868	S		[(S)-(((R)-4-Hydroxy-9-piperazin-1-ylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1869	S		[(S)-(((S)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1870	S		[(S)-(((R)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1871	S		[(S)-(((S)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1872	S		[(S)-(((R)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1873	S		[(S)-(((R)-3-(Hydroxymethyl)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1874	S		[(S)-(((S)-3-(Hydroxymethyl)nonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1875	S		[(S)-(((R)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1876	S		[(S)-(((S)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1877	S		[(S)-(((R)-3-(Hydroxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1878	S		[(S)-(((S)-3-(Hydroxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1879	S		[(S)-(((R)-3-Hydroxymethyl-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1880	S		[(S)-(((S)-3-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1881	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1882	S		[(S)-(((R)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-

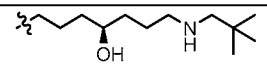
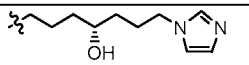
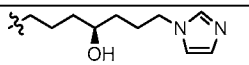
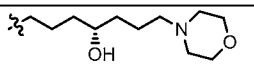
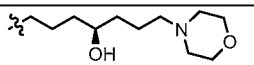
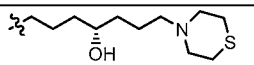
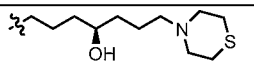
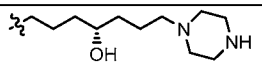
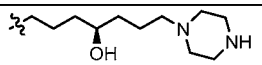
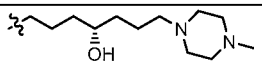
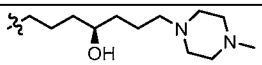
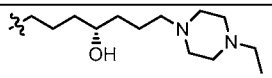
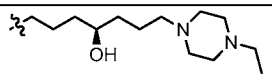
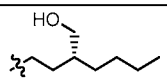
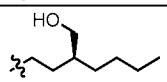
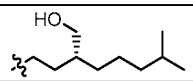
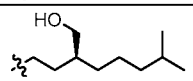
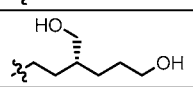
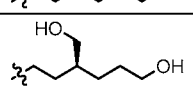
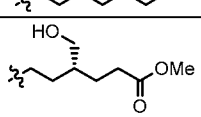
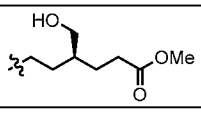
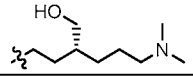
			MeLeu]-4-cyclosporin
1883	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1884	S		[(S)-(((R)-3-(Hydroxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1885	S		[(S)-(((R)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1886	S		[(S)-(((S)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1887	S		[(S)-(((R)-3-Hydroxymethyl-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1888	S		[(S)-(((S)-3-Hydroxymethyl-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1889	S		[(S)-(((R)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1890	S		[(S)-(((S)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1891	S		[(S)-(((R)-3-Hydroxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1892	S		[(S)-(((S)-3-Hydroxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1893	S		[(S)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1894	S		[(S)-(((S)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1895	S		[(S)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1896	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1897	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1898	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-isopropylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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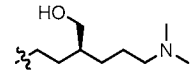
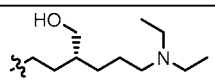
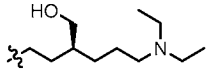
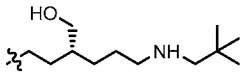
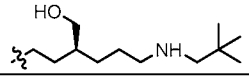
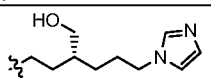
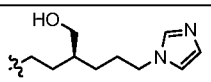
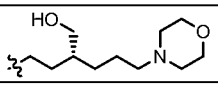
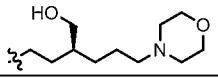
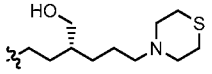
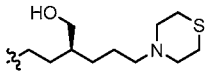
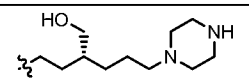
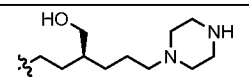
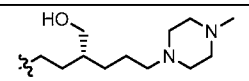
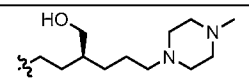
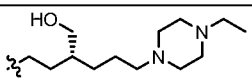
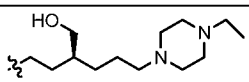
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1901	S		[(S)-(((R)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1902	S		[(S)-(((S)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1903	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1904	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1905	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1906	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1907	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1908	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1909	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1910	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1911	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1912	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1913	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1914	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1915	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1916	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

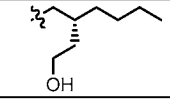
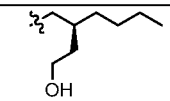
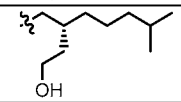
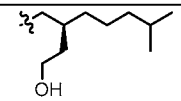
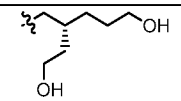
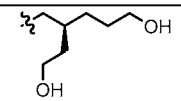
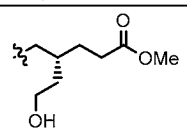
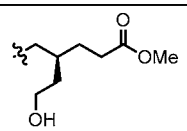
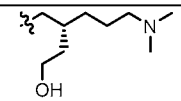
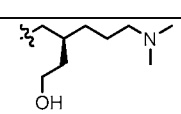
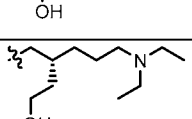
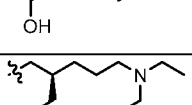
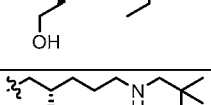
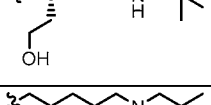
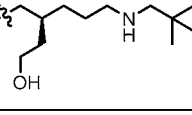
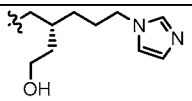
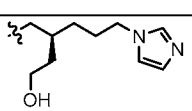
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1918	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1919	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1920	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1921	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1922	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1923	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1924	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1925	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1926	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-potassium salt
1927	S		[(S)-(9-(Ethoxycarbonyl)nonylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1928	O		[(R)-(8-(N,N-Dimethylamino)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1929	O		[(R)-(8-(N,N-Diethylamino)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1930	O		[(R)-(8-(N,N-Diisobutylamino)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1931	O		[(R)-(8-(Neopentylamino)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1932	O		[(R)-(8-(N-Methyl-N-neopentyl)amino)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1933	O		[(R)-(8-(N-Ethyl-N-neopentyl)amino)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1934	O		[(R)-(8-(1H-imidazol-1-yl)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1935	O		[(R)-(8-(Pyrrolidin-1-yl)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1936	O		[(R)-(8-(Piperidin-1-yl)octyloxy)methyl-Sar]-3-[(γ-methoxy)-

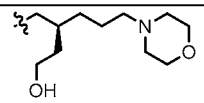
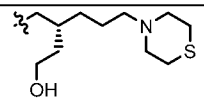
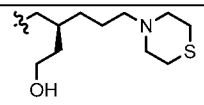
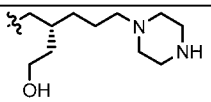
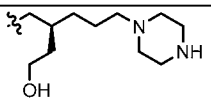
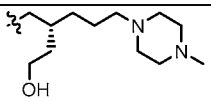
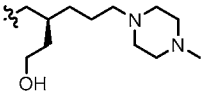
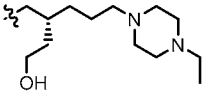
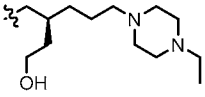
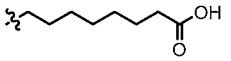
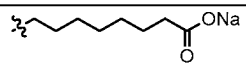
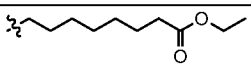
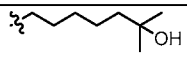
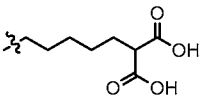
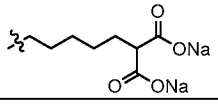
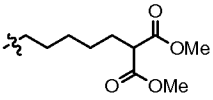
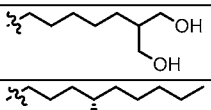
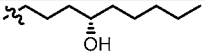
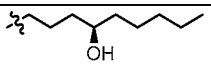
			N-MeLeu]-4-cyclosporin
1937	O		[(R)-((8-Morpholinooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1938	O		[(R)-((8-Thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1939	O		[(R)-((8-(Piperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1940	O		[(R)-((8-(4-Methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1941	O		[(R)-((8-(4-Ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1942	O		[(R)-((8-(4-Isopropylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1943	O		[(R)-((8-(4-neopentylpiperazin-1-yl)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1944	O		[(R)-(10-(N,N-Dimethylamino)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1945	O		[(R)-(10-(N,N-Diethylamino)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1946	O		[(R)-(10-(N,N-Diisobutylamino)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1947	O		[(R)-(10-(Neopentylamino)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1948	O		[(R)-(10-(methyl(neopentyl)amino)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1949	O		[(R)-(10-(Ethyl(neopentyl)amino)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1950	O		[(R)-(10-(1H-imidazol-1-yl)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1951	O		[(R)-(10-(Pyrrolidin-1-yl)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1952	O		[(R)-(10-(Piperidin-1-yl)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1953	O		[(R)-((10-Morpholinodecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1954	O		[(R)-((10-Thiomorpholinodecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1955	O		[(R)-((10-(Piperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1956	O		[(R)-((10-(4-Methylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1957	O		[(R)-((10-(4-Ethylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1958	O		[(R)-((10-(4-Isopropylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1959	O		[(R)-((10-(4-Neopentylpiperazin-1-yl)decyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

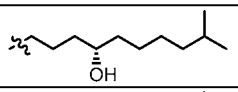
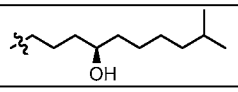
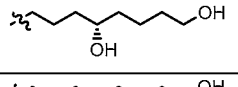
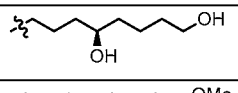
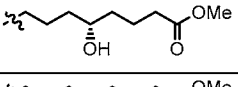
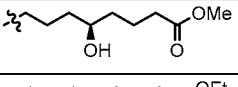
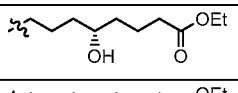
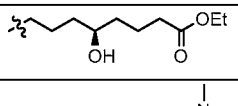
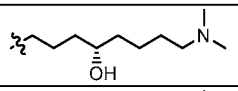
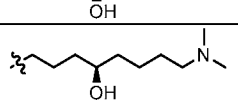
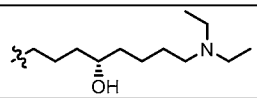
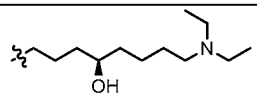
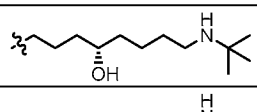
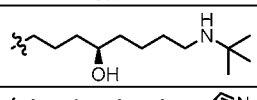
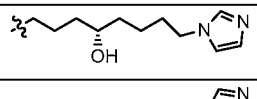
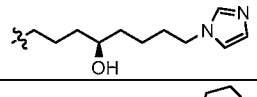
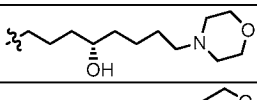
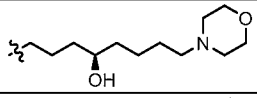
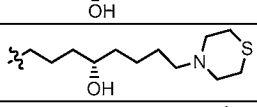
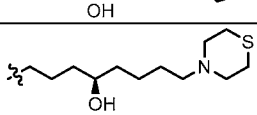
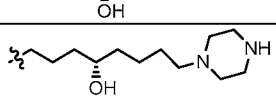
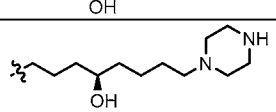
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1961	O		[(R)-(6-Carboxyhexyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-sodium salt
1962	O		[(R)-(6-(Ethoxycarbonyl)hexyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1963	O		[(R)-((5-Hydroxy-5-methylhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1964	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1965	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin- disodium salt
1966	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1967	O		[(R)-((6-Methoxy-5-(methoxycarbonyl)-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1968	O		[(R)-((6-Hydroxy-5-hydroxymethylhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1969	O		[(R)-(((S)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1970	O		[(R)-((R)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1971	O		[(R)-((S)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1972	O		[(R)-((R)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1973	O		[(R)-((S)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1974	O		[(R)-((R)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1975	O		[(R)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1976	O		[(R)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1977	O		[(R)-(((S)-4-Hydroxy-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1978	O		[(R)-(((R)-4-Hydroxy-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1979	O		[(R)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1980	O		[(R)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1981	O		[(R)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

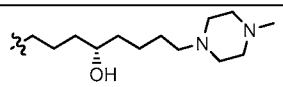
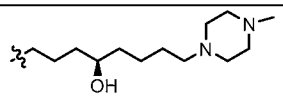
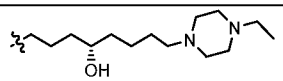
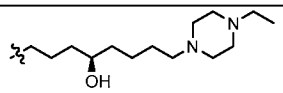
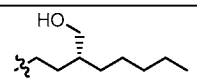
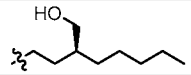
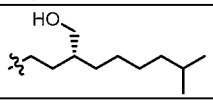
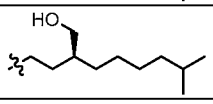
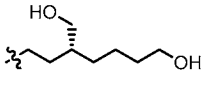
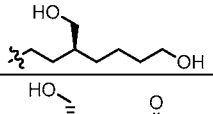
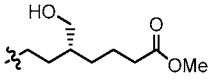
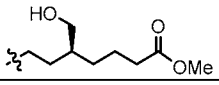
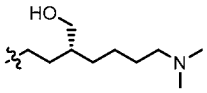
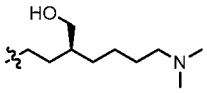
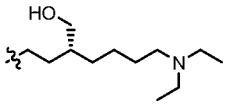
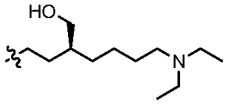
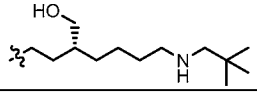
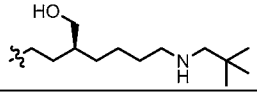
1982	O		[(R)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1983	O		[(R)-(((S)-4-Hydroxy-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1984	O		[(R)-(((R)-4-Hydroxy-7-(imidazo-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1985	O		[(R)-(((S)-4-Hydroxy-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1986	O		[(R)-(((R)-4-Hydroxy-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1987	O		[(R)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1988	O		[(R)-(((R)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1989	O		[(R)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1990	O		[(R)-(((R)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1991	O		[(R)-(((S)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1992	O		[(R)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl)heptyl) oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1993	O		[(R)-(((S)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptylcyclos)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1994	O		[(R)-(((R)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1995	O		[(R)-(((R)-3-(Hydroxymethyl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1996	O		[(R)-(((S)-3-(Hydroxymethyl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1997	O		[(R)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1998	O		[(R)-(((S)-3-(Hydroxymethyl)-7-methyloctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
1999	O		[(R)-(((R)-3-(Hydroxymethyl)-6-hydroxyhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2000	O		[(R)-(((S)-3-(Hydroxymethyl)-6-hydroxyhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2001	O		[(R)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2002	O		[(R)-(((S)-3-Hydroxy-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2003	O		[(R)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-

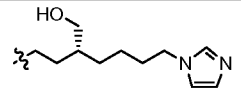
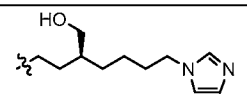
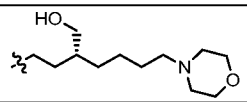
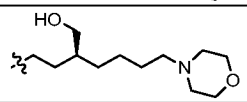
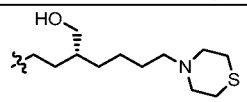
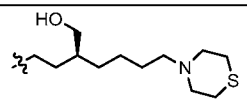
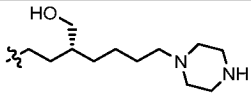
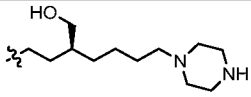
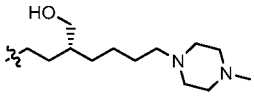
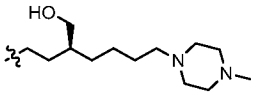
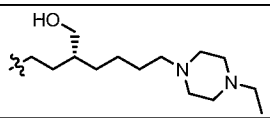
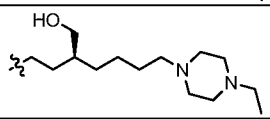
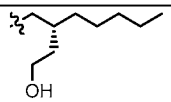
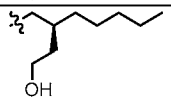
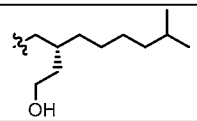
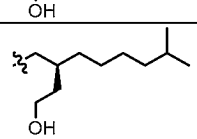
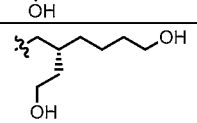
			MeLeu]-4-cyclosporin
2004	O		[(R)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2005	O		[(R)-(((R)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2006	O		[(R)-(((S)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2007	O		[(R)-(((R)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2008	O		[(R)-(((S)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2009	O		[(R)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2010	O		[(R)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2011	O		[(R)-(((R)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2012	O		[(R)-(((S)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2013	O		[(R)-(((R)-3-Hydroxymethyl-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2014	O		[(R)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2015	O		[(R)-(((R)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2016	O		[(R)-(((S)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2017	O		[(R)-(((R)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2018	O		[(R)-(((S)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2019	O		[(R)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2020	O		[(R)-(((S)-3-Hydroxymethyl-6-(4-isopropylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

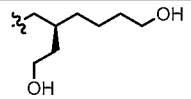
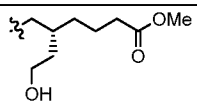
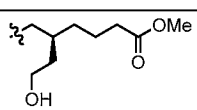
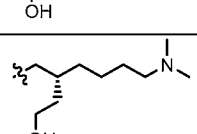
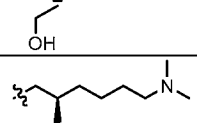
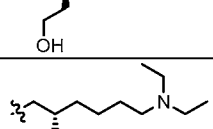
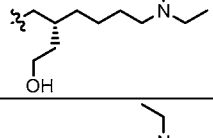
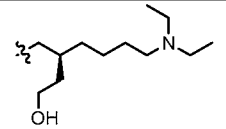
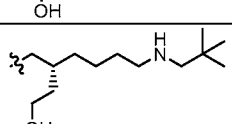
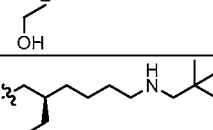
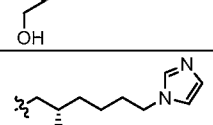
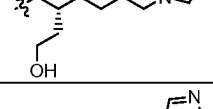
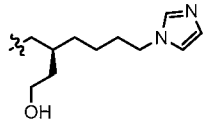
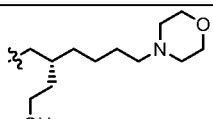
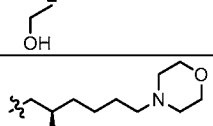
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2022	O		[(R)-(((S)-2-(2-Hydroxyethyl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2023	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2024	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2025	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2026	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2027	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2028	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2029	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2030	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2031	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2032	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2033	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2034	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2035	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2036	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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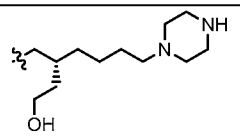
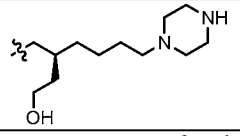
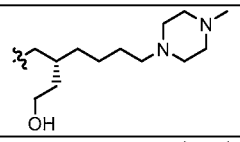
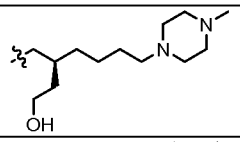
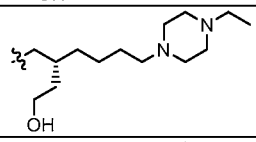
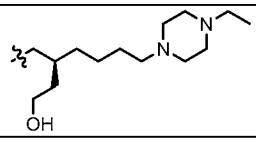
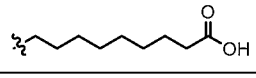
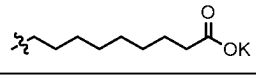
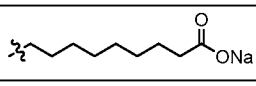
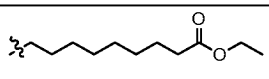
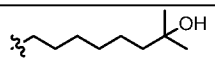
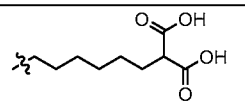
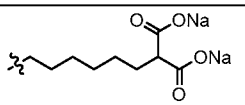
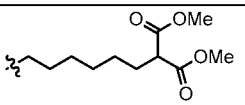
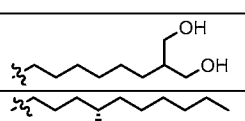
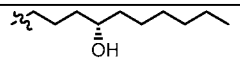
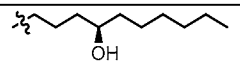
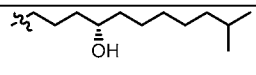
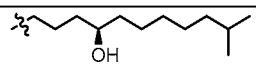
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2039	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2040	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2041	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2042	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2043	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2044	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2045	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2046	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2047	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2048	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-sodium salt
2049	O		[(R)-(7-(Ethoxycarbonyl)heptyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2050	O		[(R)-((6-Hydroxy-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2051	O		[(R)-((6,6'-Dicarboxy)hexyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2052	O		[(R)-((6,6'-Dicarboxy)hexyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin- disodium salt
2053	O		[(R)-((7-Methoxy-6-(methoxycarbonyl)-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2054	O		[(R)-((7-Hydroxy-6-hydroxymethylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2055	O		[(R)-((S)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2056	O		[(R)-((R)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

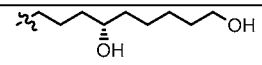
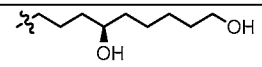
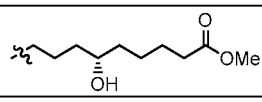
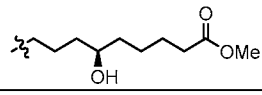
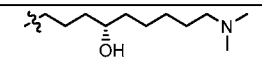
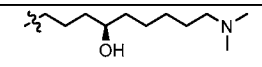
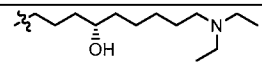
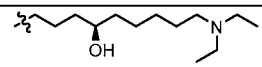
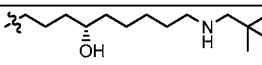
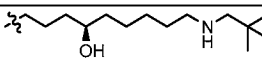
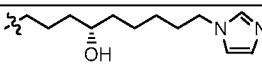
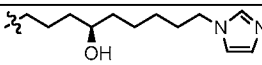
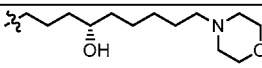
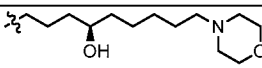
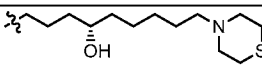
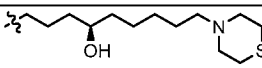
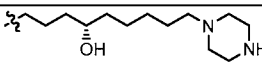
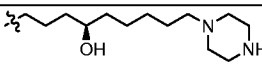
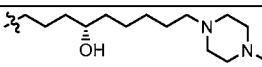
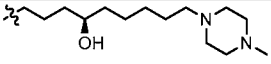
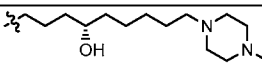
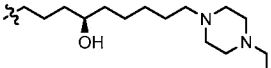
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2065	O		[(R)-(((S)-4-Hydroxy-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2071	O		[(R)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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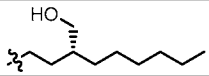
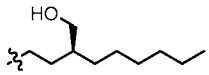
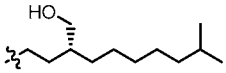
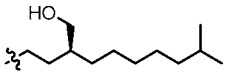
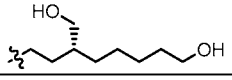
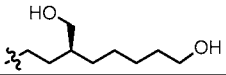
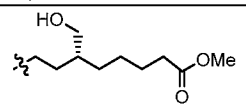
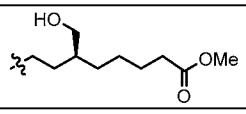
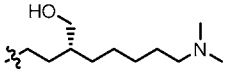
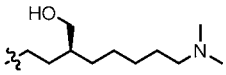
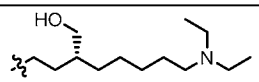
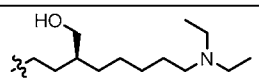
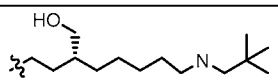
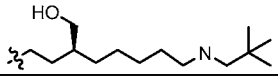
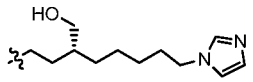
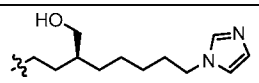
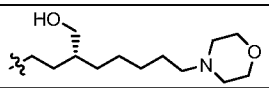
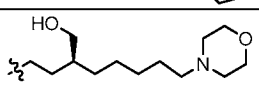
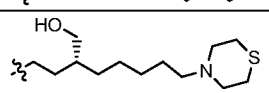
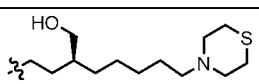
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2081	O		[(R)-(((S)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2082	O		[(R)-(((R)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2086	O		[(R)-(((S)-3-(Hydroxymethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2087	O		[(R)-((((R)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2089	O		[(R)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2092	O		[(R)-((((S)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2095	O		[(R)-(((R)-3-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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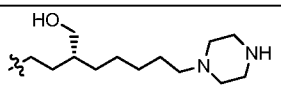
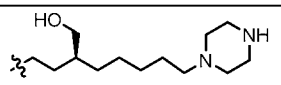
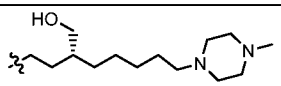
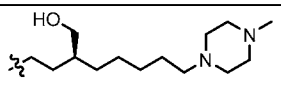
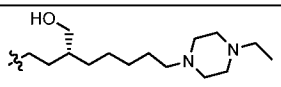
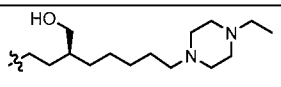
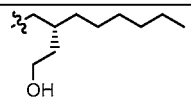
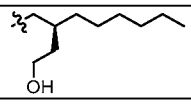
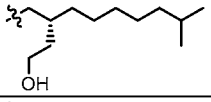
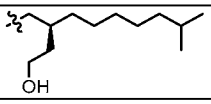
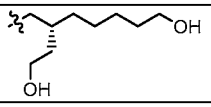
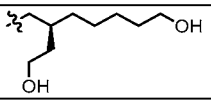
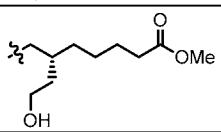
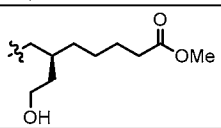
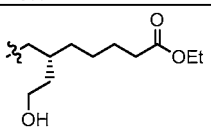
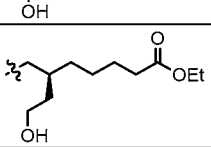
2097	O		[(R)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2098	O		[(R)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2099	O		[(R)-(((R)-3-Hydroxymethyl-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2100	O		[(R)-(((S)-3-Hydroxymethyl-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2101	O		[(R)-(((R)-3-Hydroxymethyl-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2102	O		[(R)-(((S)-3-Hydroxymethyl-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2103	O		[(R)-(((R)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2104	O		[(R)-(((S)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2105	O		[(R)-(((R)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2106	O		[(R)-(((S)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2107	O		[(R)-(((R)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2108	O		[(R)-(((S)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2109	O		[(R)-(((R)-2-(2-Hydroxyethyl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2110	O		[(R)-(((S)-2-(2-Hydroxyethyl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2111	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-methyoctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2112	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-methyoctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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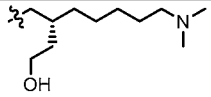
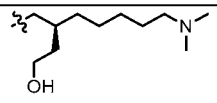
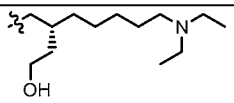
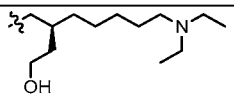
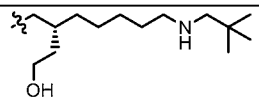
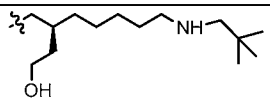
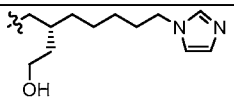
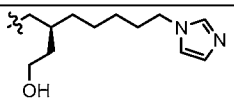
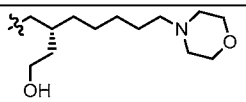
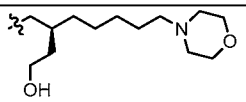
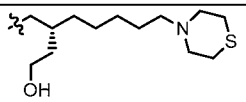
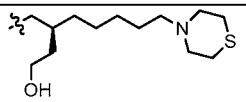
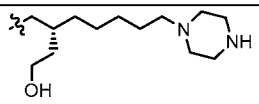
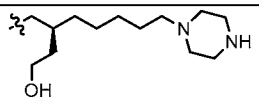
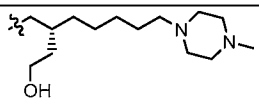
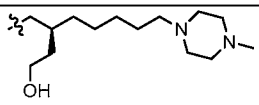
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2115	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2116	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2117	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2118	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2119	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2120	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2121	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2122	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(neopentylamino)hepxyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2123	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(imidazol-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2124	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(imidazo-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2125	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2126	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2127	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2128	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

2129	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2130	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2131	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2132	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2133	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(4-ethylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2134	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(4-isopropylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2135	O		[(R)-(8-Carboxyoctyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2136	O		[(R)-(8-Carboxyoctyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-potassium salt
2137	O		[(R)-(8-Carboxyoctyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-potassium salt
2138	O		[(R)-(8-(Ethoxycarbonyl)octyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2139	O		[(R)-((7-Hydroxy-7-methyloctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2140	O		[(R)-((7,7'-Dicarboxy)heptyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2141	O		[(R)-((7,7'-Dicarboxy)heptyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin- disodium salt
2142	O		[(R)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2143	O		[(R)-((8-Hydroxy-7-hydroxymethyloctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2144	O		[(R)-(((S)-4-Hydroxydecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2145	O		[(R)-(((R)-4-Hydroxydecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2146	O		[(R)-(((S)-4-Hydroxy-10-methylundecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2147	O		[(R)-(((R)-4-Hydroxy-10-methylundecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

2148	O		[(R)-(((S)-4,9-Dihydroxynonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2149	O		[(R)-(((R)-4,9-Dihydroxynonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2150	O		[(R)-(((S)-4-Hydroxy-9-methoxy-9-oxononyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2151	O		[(R)-(((R)-4-Hydroxy-9-methoxy-9-oxononyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2152	O		[(R)-(((S)-4-Hydroxy-9-(dimethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2153	O		[(R)-(((R)-4-Hydroxy-9-(dimethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2154	O		[(R)-(((S)-4-Hydroxy-9-(diethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2155	O		[(R)-(((R)-4-Hydroxy-9-(diethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2156	O		[(R)-(((S)-4-Hydroxy-9-(neopentylamino)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2157	O		[(R)-(((R)-4-Hydroxy-9-(neopentylamino)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2158	O		[(R)-(((S)-4-Hydroxy-9-(imidazol-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2159	O		[(R)-(((R)-4-Hydroxy-9-(imidazo-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2160	O		[(R)-(((S)-4-Hydroxy-9-morpholinononyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2161	O		[(R)-(((R)-4-Hydroxy-9-morpholinononyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2162	O		[(R)-(((S)-4-Hydroxy-9-thiomorpholinononyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2163	O		[(R)-(((R)-4-Hydroxy-9-thiomorpholinononyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2164	O		[(R)-(((S)-4-Hydroxy-9-piperazin-1-ylnonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2165	O		[(R)-(((R)-4-Hydroxy-9-piperazin-1-ylnonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2166	O		[(R)-(((S)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2167	O		[(R)-(((R)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2168	O		[(R)-(((S)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2169	O		[(R)-(((R)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

2170	O		[(R)-(((R)-3-(Hydroxymethyl)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2171	O		[(R)-(((S)-3-(Hydroxymethyl)nonyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2172	O		[(R)-(((R)-3-(Hydroxymethyl)-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2173	O		[(R)-(((S)-3-(Hydroxymethyl)-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2174	O		[(R)-(((R)-3-(Hydroxymethyl)-8-hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2175	O		[(R)-(((S)-3-(Hydroxymethyl)-8-hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2176	O		[(R)-(((R)-3-Hydroxymethyl-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2177	O		[(R)-(((S)-3-Hydroxy-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2178	O		[(R)-(((S)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2179	O		[(R)-(((R)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2181	O		[(R)-(((R)-3-(Hydroxymethyl)-8-(diethylamino)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2182	O		[(R)-(((R)-3-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2183	O		[(R)-(((S)-3-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2184	O		[(R)-(((R)-3-Hydroxymethyl-8-(imidazol-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2185	O		[(R)-(((S)-3-Hydroxymethyl-8-(imidazo-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2186	O		[(R)-(((R)-3-Hydroxymethyl-8-morpholinooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2188	O		[(R)-(((R)-3-Hydroxymethyl-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2189	O		[(R)-(((S)-3-Hydroxymethyl-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-

			MeLeu]-4-cyclosporin
2190	O		[(R)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2191	O		[(R)-(((S)-3-Hydroxymethyl-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2192	O		[(R)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2193	O		[(R)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2194	O		[(R)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2201	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2202	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2203	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2204	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-ethoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2205	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-ethoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

2206	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2206	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2207	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2208	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2209	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2210	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2211	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2212	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2213	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
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2215	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2216	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2217	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2218	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2219	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2220	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

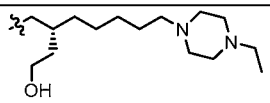
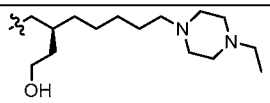
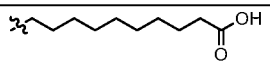
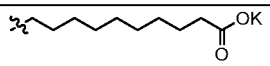
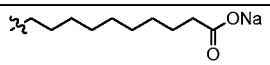
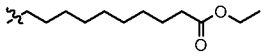
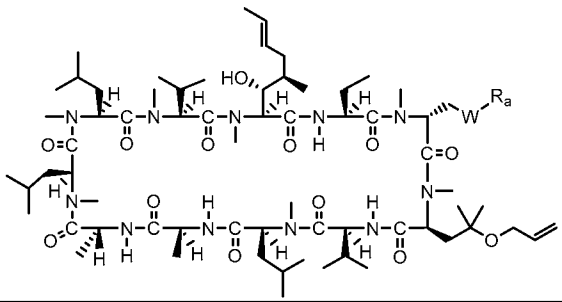
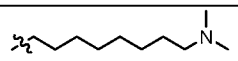
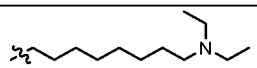
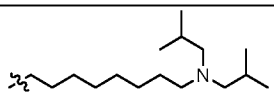
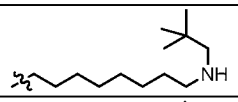
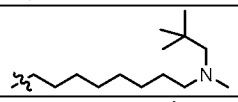
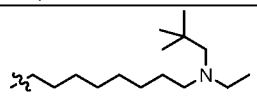
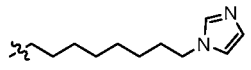
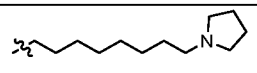
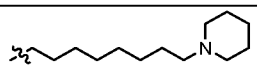
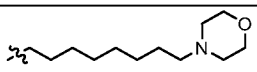
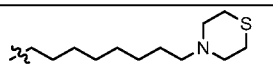
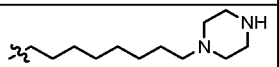
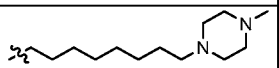
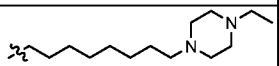
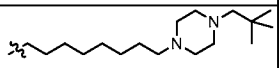
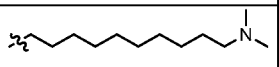
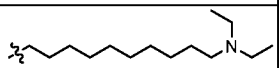
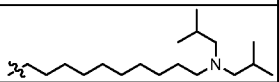
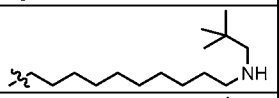
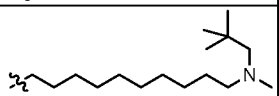
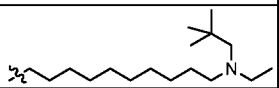
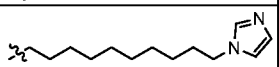
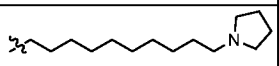
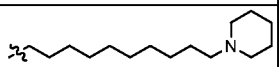
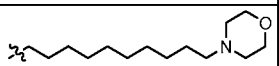
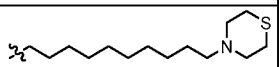
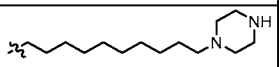
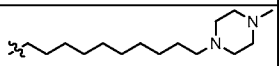
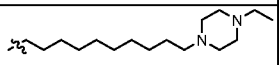
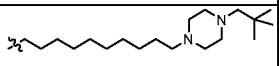
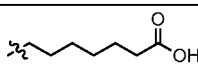
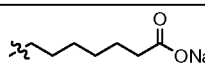
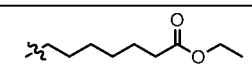
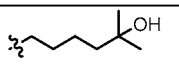
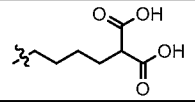
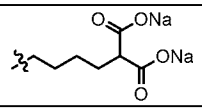
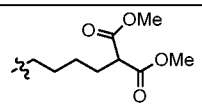
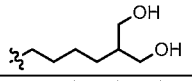
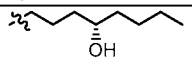
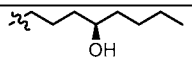
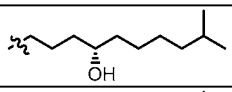
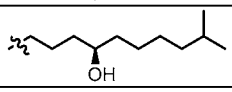
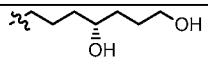
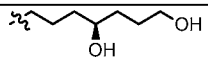
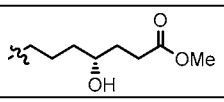
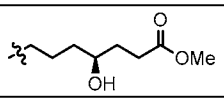
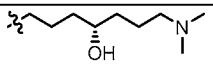
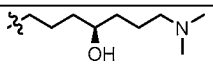
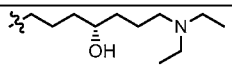
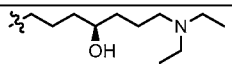
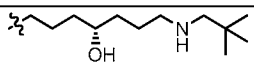
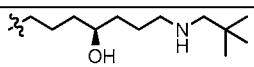
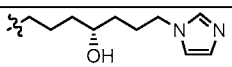
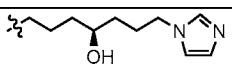
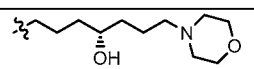
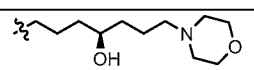
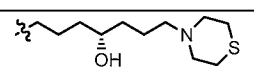
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2222	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2223	O		[(R)-(9-Carboxynonyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin
2224	O		[(R)-(9-Carboxynonyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-potassium salt
2225	O		[(R)-(9-Carboxynonyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin-potassium salt
2226	O		[(R)-(9-(Ethoxycarbonyl)nonyloxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin

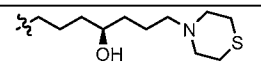
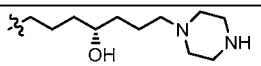
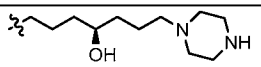
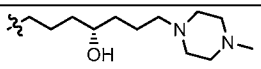
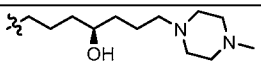
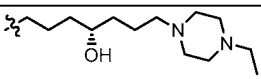
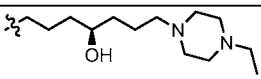
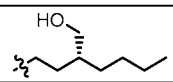
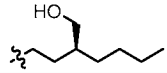
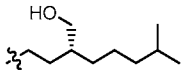
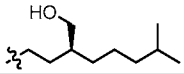
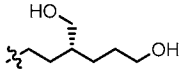
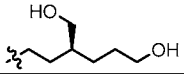
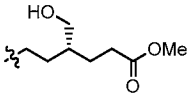
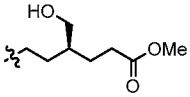
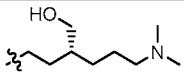
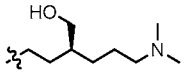
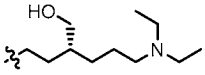
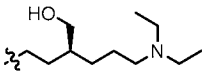
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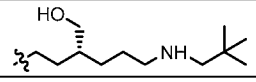
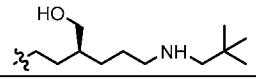
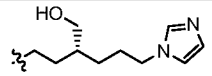
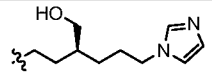
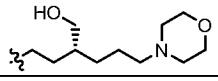
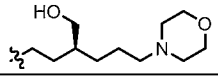
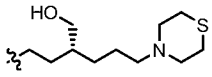
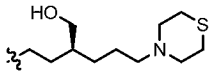
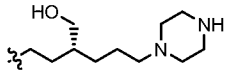
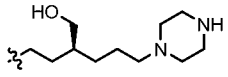
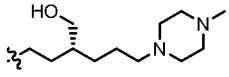
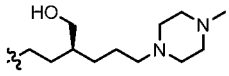
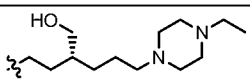
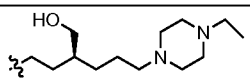
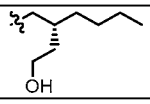
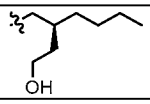
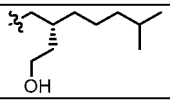
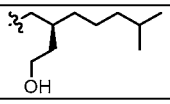


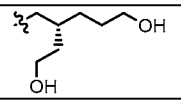
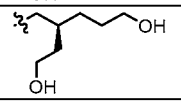
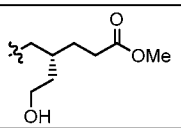
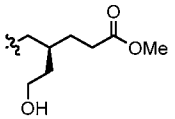
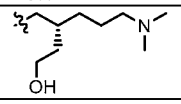
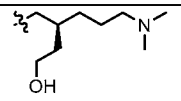
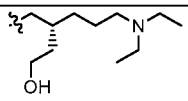
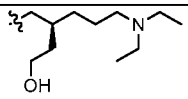
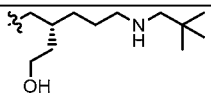
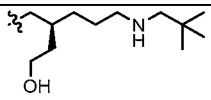
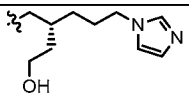
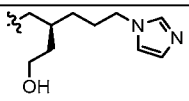
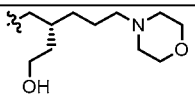
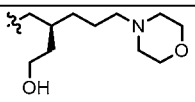
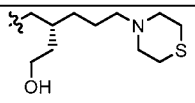
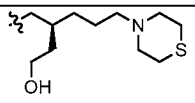
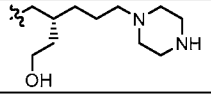
Ex. No.	W	R_a	Name
2227	S		[(S)-(8-(N,N-Dimethylamino)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2228	S		[(S)-(8-(N,N-Diethylamino)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2229	S		[(S)-(8-(N,N-Diisobutylamino)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2230	S		[(S)-(8-(Neopentylamino)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2231	S		[(S)-(8-(N-Methyl-N-neopentyl)amino)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2232	S		[(S)-(8-(N-Ethyl-N-neopentyl)amino)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2233	S		[(S)-(8-(1H-imidazol-1-yl)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2234	S		[(S)-(8-(Pyrrolidin-1-yl)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2235	S		[(S)-(8-(Piperidin-1-yl)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2236	S		[(S)-((8-Morpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

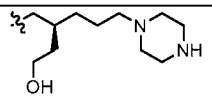
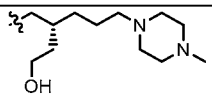
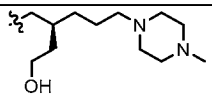
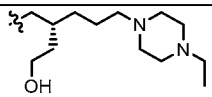
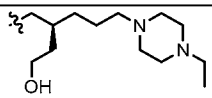
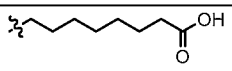
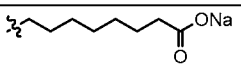
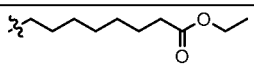
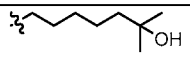
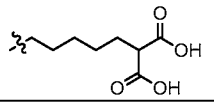
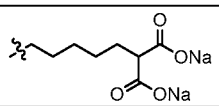
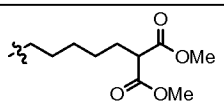
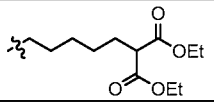
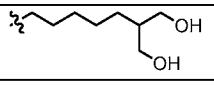
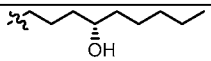
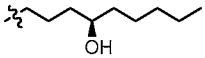
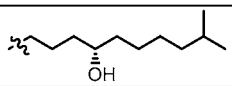
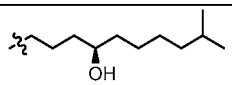
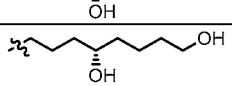
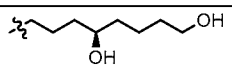
2237	S		[(S)-((8-Thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2238	S		[(S)-((8-(Piperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2239	S		[(S)-((8-(4-Methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2240	S		[(S)-((8-(4-Ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2241	S		[(S)-((8-(4-Neopentylpiperazin-1-yl)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2242	S		[(S)-(10-(N,N-Dimethylamino)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2243	S		[(S)-(10-(N,N-Diethylamino)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2244	S		[(S)-(10-(N,N-Diisobutylamino)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2245	S		[(S)-(10-(Neopentylamino)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2246	S		[(S)-(10-(N-Methyl-N-neopentyl)amino)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2247	S		[(S)-(10-(N-Ethyl-N-neopentyl)amino)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2248	S		[(S)-(10-(1H-imidazol-1-yl)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2249	S		[(S)-(10-(Pyrrolidin-1-yl)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2250	S		[(S)-(10-(Piperidin-1-yl)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2251	S		[(S)-((10-Morpholinodecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2252	S		[(S)-((10-Thiomorpholinodecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2253	S		[(S)-((10-(Piperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2254	S		[(S)-((10-(4-Methylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2255	S		[(S)-((10-(4-Ethylpiperazin-1-yl)decyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2256	S		[(S)-((8-(4-Neopentylpiperazin-1-yl)decylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2257	S		[(S)-(6-Carboxyhexylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2258	S		[(S)-(6-Carboxyhexylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin-sodium salt
2259	S		[(S)-(6-(Ethoxycarbonyl)hexylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2260	S		[(S)-((5-Hydroxy-5-methylhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

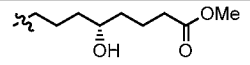
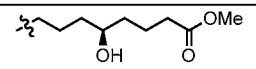
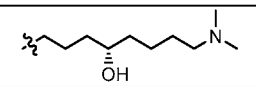
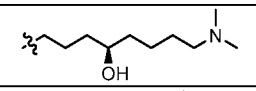
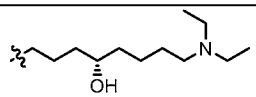
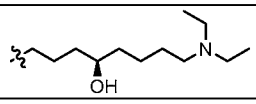
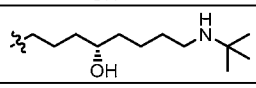
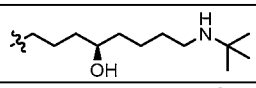
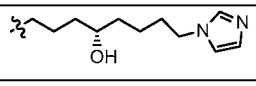
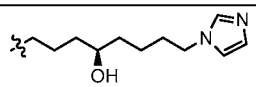
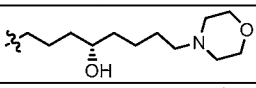
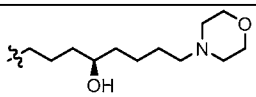
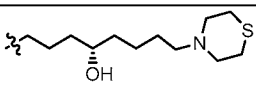
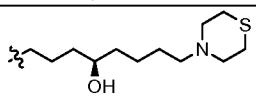
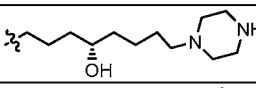
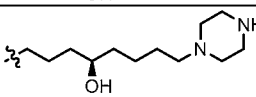
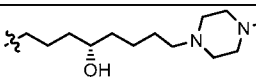
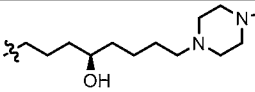
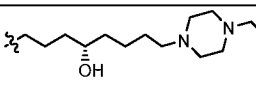
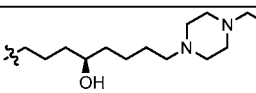
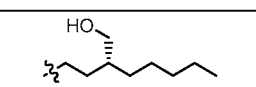
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2262	S		[(S)-((5,5'-Dicarboxy)pentylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin- disodium salt
2263	S		[(S)-((6-Methoxy-5-(methoxycarbonyl)-6-oxohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2264	S		[(S)-((6-Hydroxy-5-hydroxymethylhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2265	S		[(S)-((S)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2266	S		[(S)-((R)-(4-Hydroxyoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2267	S		[(S)-((S)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2268	S		[(S)-((R)-4-Hydroxy-8-methylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2269	S		[(S)-((S)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2270	S		[(S)-((R)-4,7-Dihydroxyheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2271	S		[(S)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2272	S		[(S)-(((R)-4-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2273	S		[(S)-(((S)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2274	S		[(S)-(((R)-4-Hydroxy-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2275	S		[(S)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2276	S		[(S)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2277	S		[(S)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2278	S		[(S)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2279	S		[(S)-(((S)-4-Hydroxy-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2280	S		[(S)-(((R)-4-Hydroxy-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2281	S		[(S)-(((S)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2282	S		[(S)-(((R)-4-Hydroxy-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2283	S		[(S)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)thio)methyl-

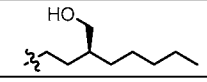
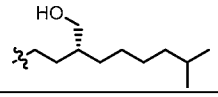
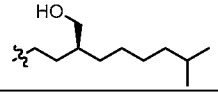
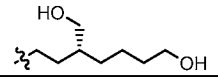
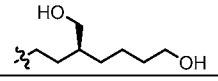
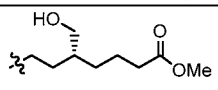
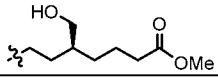
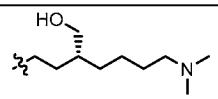
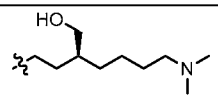
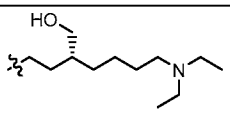
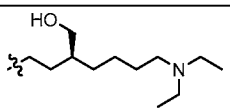
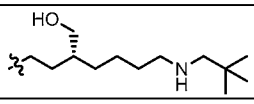
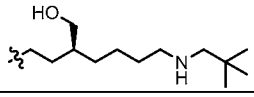
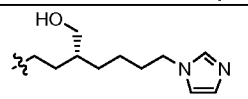
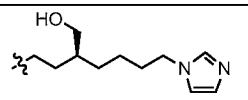
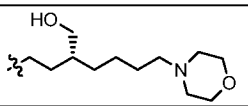
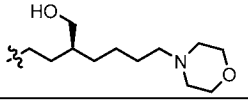
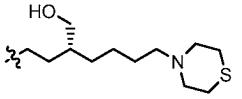
			Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2284	S		[(S)-(((R)-4-Hydroxy-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2285	S		[(S)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2286	S		[(S)-(((R)-4-Hydroxy-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2287	S		[(S)-(((S)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2288	S		[(S)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2289	S		[(S)-(((S)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2290	S		[(S)-(((R)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2291	S		[(S)-(((R)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2292	S		[(S)-(((S)-3-(Hydroxymethyl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2293	S		[(S)-(((R)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2294	S		[(S)-(((S)-3-(Hydroxymethyl)-7-methyloctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2295	S		[(S)-(((R)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2296	S		[(S)-(((S)-3-(Hydroxymethyl)-6-hydroxyhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2297	S		[(S)-(((R)-3-Hydroxymethyl-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2298	S		[(S)-(((S)-3-Hydroxy-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2299	S		[(S)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2300	S		[(S)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2301	S		[(S)-(((R)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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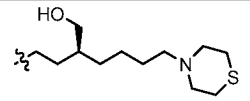
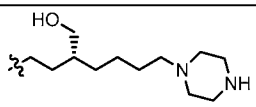
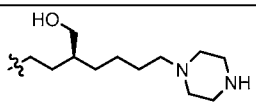
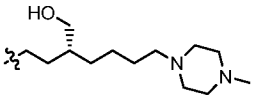
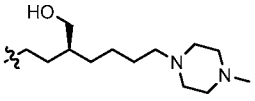
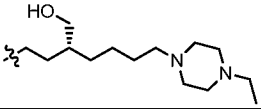
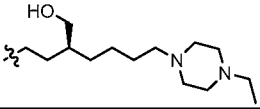
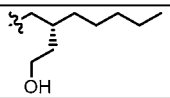
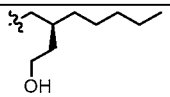
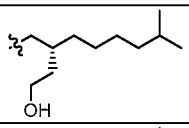
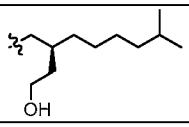
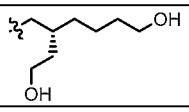
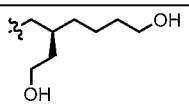
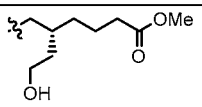
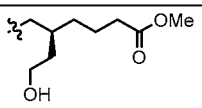
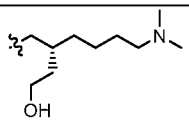
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2304	S		[(S)-(((S)-3-Hydroxy-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2305	S		[(S)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2306	S		[(S)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2307	S		[(S)-(((R)-3-Hydroxymethyl-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2308	S		[(S)-(((S)-3-Hydroxymethyl-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2309	S		[(S)-(((R)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2310	S		[(S)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2311	S		[(S)-(((R)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2312	S		[(S)-(((S)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2313	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2314	S		[(S)-(((S)-3-Hydroxymethyl-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2315	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2316	S		[(S)-(((S)-3-Hydroxymethyl-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2317	S		[(S)-(((R)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2318	S		[(S)-(((S)-2-(2-Hydroxyethyl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2319	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2320	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-methylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

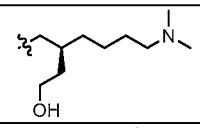
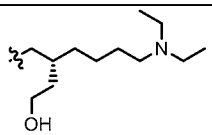
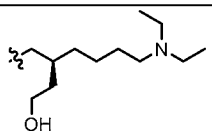
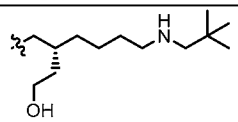
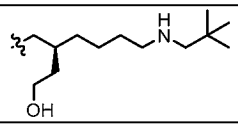
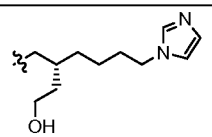
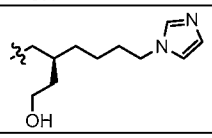
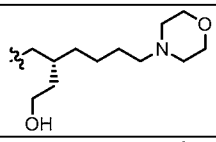
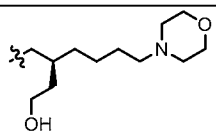
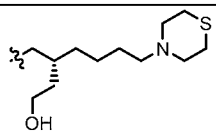
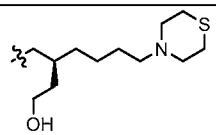
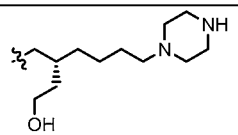
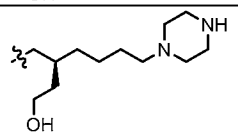
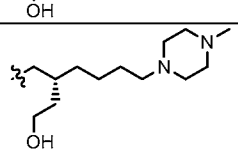
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2322	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2323	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2324	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2325	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-cyclosporin
2326	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2327	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2328	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2329	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2330	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2331	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2332	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2333	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2334	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2335	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2336	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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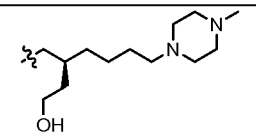
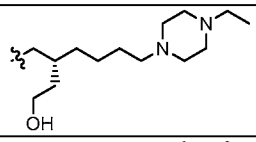
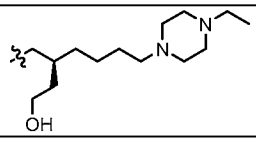
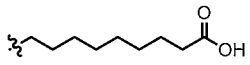
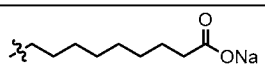
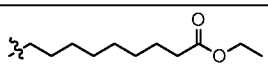
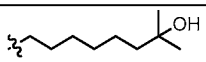
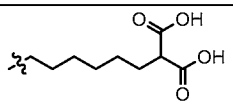
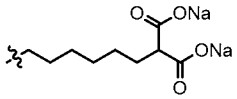
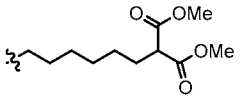
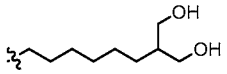
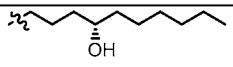
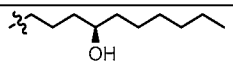
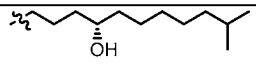
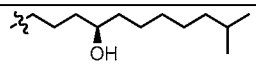
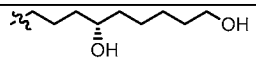
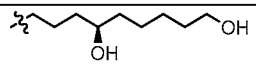
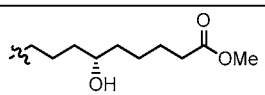
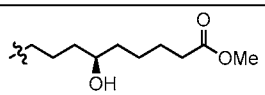
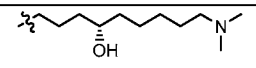
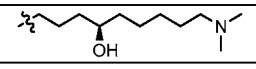
			cyclosporin
2338	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2339	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2340	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2341	S		[(S)-(((R)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2342	S		[(S)-(((S)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2343	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2344	S		[(S)-(7-Carboxyheptylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin-sodium salt
2345	S		[(S)-(7-(Ethoxycarbonyl)heptylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2346	S		[(S)-((6-Hydroxy-6-methylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2347	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2348	S		[(S)-((6,6'-Dicarboxy)hexylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin- disodium salt
2349	S		[(S)-((7-Methoxy-6-(methoxycarbonyl)-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2350	S		[(S)-((7-Ethoxy-6-(ethoxycarbonyl)-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2351	S		[(S)-((7-Hydroxy-6-hydroxymethylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2352	S		[(S)-((S)-(4-Hydroxynonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2353	S		[(S)-((R)-(4-Hydroxynonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2354	S		[(S)-((S)-4-Hydroxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2355	S		[(S)-((R)-4-Hydroxy-9-methyldecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2356	S		[(S)-(((S)-4,8-Dihydroxyoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2357	S		[(S)-(((R)-4,8-Dihydroxyoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

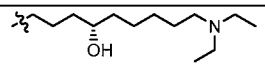
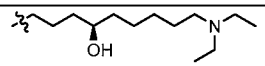
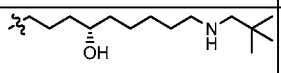
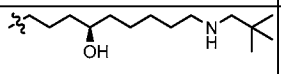
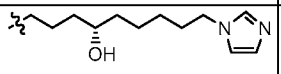
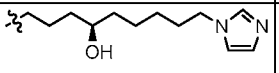
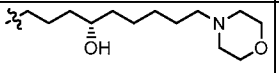
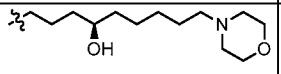
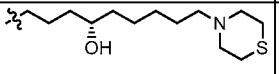
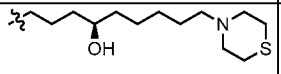
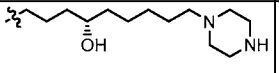
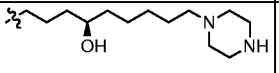
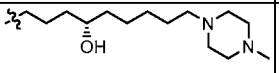
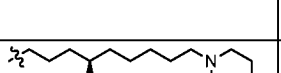
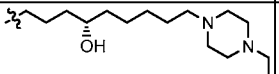
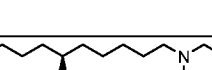
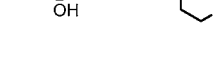
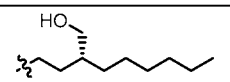
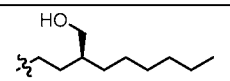
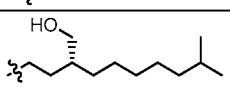
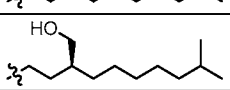
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2359	S		[(S)-(((R)-4-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2360	S		[(S)-(((S)-4-Hydroxy-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2361	S		[(S)-(((R)-4-Hydroxy-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2362	S		[(S)-(((S)-4-Hydroxy-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2363	S		[(S)-(((R)-4-Hydroxy-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2364	S		[(S)-(((S)-4-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2365	S		[(S)-(((R)-4-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2366	S		[(S)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2367	S		[(S)-(((R)-4-Hydroxy-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2368	S		[(S)-(((S)-4-Hydroxy-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2369	S		[(S)-(((R)-4-Hydroxy-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2370	S		[(S)-(((S)-4-Hydroxy-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2371	S		[(S)-(((R)-4-Hydroxy-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2372	S		[(S)-(((S)-4-Hydroxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2373	S		[(S)-(((R)-4-Hydroxy-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2374	S		[(S)-(((S)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2375	S		[(S)-(((R)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2376	S		[(S)-(((S)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2377	S		[(S)-(((R)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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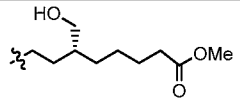
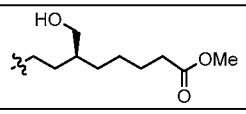
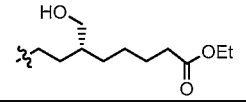
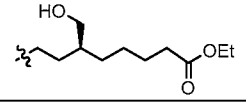
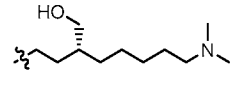
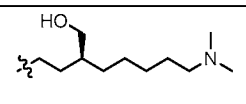
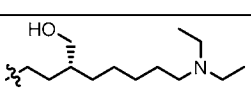
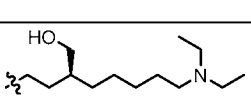
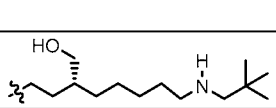
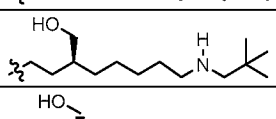
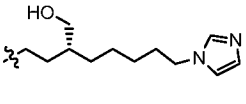
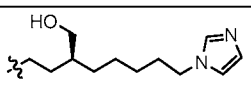
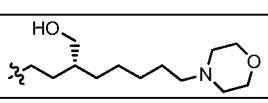
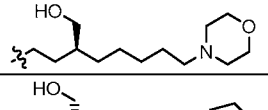
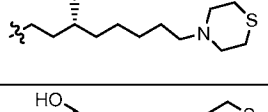
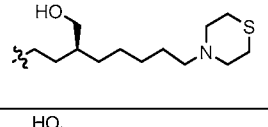
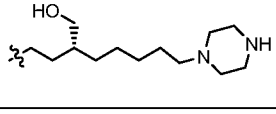
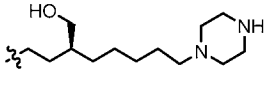
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2380	S		[(S)-(((R)-3-(Hydroxymethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2381	S		[(S)-(((S)-3-(Hydroxymethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2382	S		[(S)-((((R)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2383	S		[(S)-((((S)-3-(Hydroxymethyl)-7-hydroxyl)hepyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2384	S		[(S)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2385	S		[(S)-(((S)-3-Hydroxy-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2386	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2387	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2388	S		[(S)-((((R)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2389	S		[(S)-((((S)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2390	S		[(S)-(((R)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2391	S		[(S)-(((S)-3-Hydroxy-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2392	S		[(S)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2393	S		[(S)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2394	S		[(S)-(((R)-3-Hydroxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2395	S		[(S)-(((S)-3-Hydroxymethyl-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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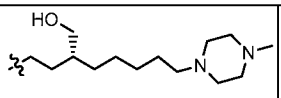
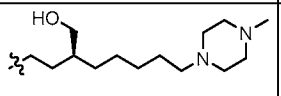
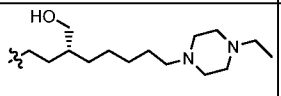
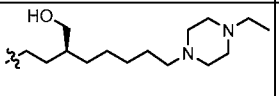
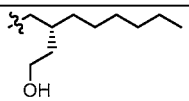
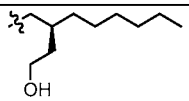
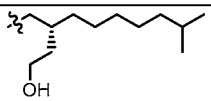
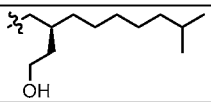
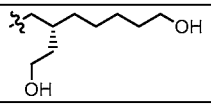
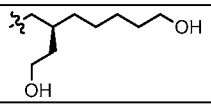
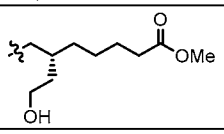
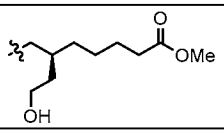
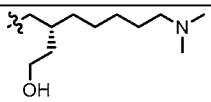
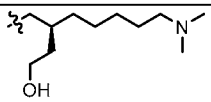
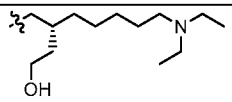
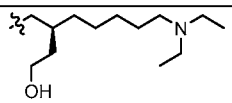
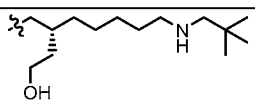
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2398	S		[(S)-(((R)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2399	S		[(S)-(((S)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2400	S		[(S)-(((R)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2401	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2402	S		[(S)-(((R)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2403	S		[(S)-(((S)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2404	S		[(S)-(((R)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2405	S		[(S)-(((S)-2-(2-Hydroxyethyl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2406	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2407	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-methyoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2408	S		[(S)-((((R)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2409	S		[(S)-((((S)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2410	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2411	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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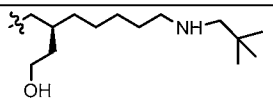
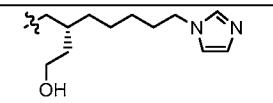
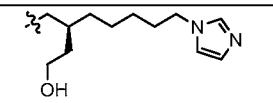
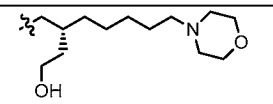
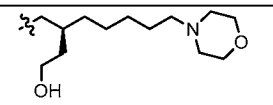
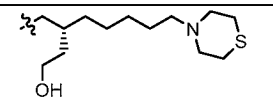
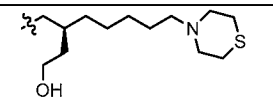
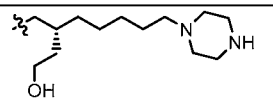
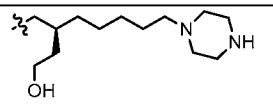
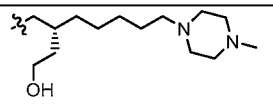
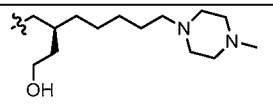
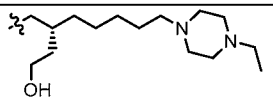
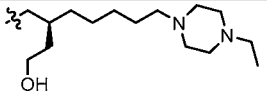
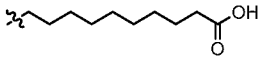
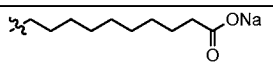
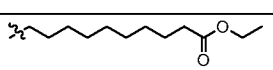
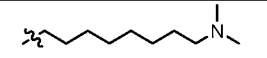
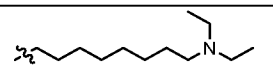
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2414	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2415	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2416	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(neopentylamino)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2417	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(neopentylamino)hepxyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2418	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(imidazol-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2419	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(imidazo-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2420	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2421	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-morpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2422	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2423	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2424	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2425	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2426	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

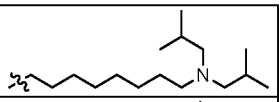
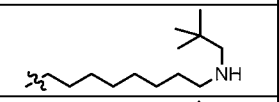
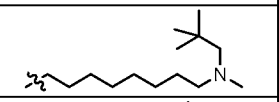
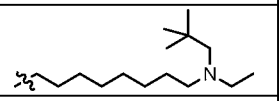
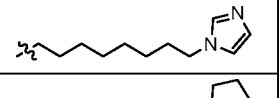
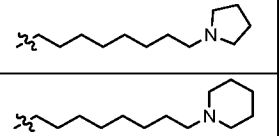
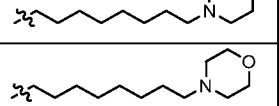
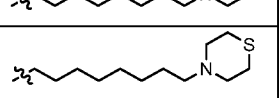
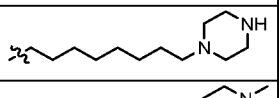
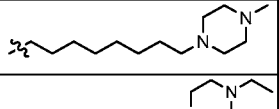
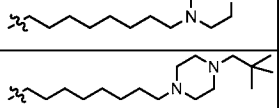
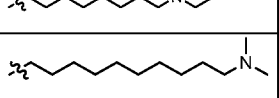
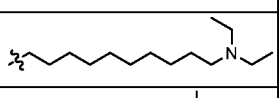
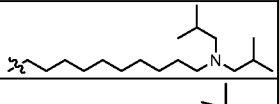
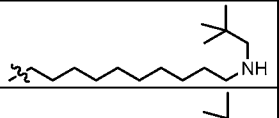
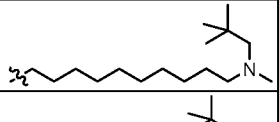
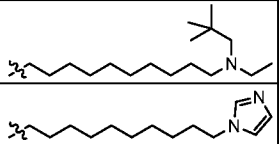
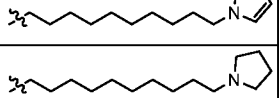
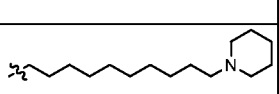
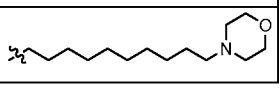
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2428	S		[(S)-(((R)-2-(2-Hydroxyethyl)-6-(4-ethylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2429	S		[(S)-(((S)-2-(2-Hydroxyethyl)-6-(4-isopropylpiperazin-1-yl)hexyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2430	S		[(S)-(8-Carboxyoctylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2431	S		[(S)-(8-Carboxyoctylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin-potassium salt
2432	S		[(S)-(8-(Ethoxycarbonyl)octylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2433	S		[(S)-((7-Hydroxy-7-methyloctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2434	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2435	S		[(S)-((7,7'-Dicarboxy)heptylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin- disodium salt
2436	S		[(S)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2437	S		[(S)-((8-Hydroxy-7-hydroxymethyloctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2438	S		[(S)-(((S)-4-Hydroxydecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2439	S		[(S)-(((R)-4-Hydroxydecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2440	S		[(S)-(((S)-4-Hydroxy-10-methylundecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2441	S		[(S)-(((R)-4-Hydroxy-10-methylundecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2442	S		[(S)-(((S)-4,9-Dihydroxynonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2443	S		[(S)-(((R)-4,9-Dihydroxynonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2444	S		[(S)-(((S)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2445	S		[(S)-(((R)-4-Hydroxy-9-methoxy-9-oxononyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2446	S		[(S)-(((S)-4-Hydroxy-9-(dimethylamino)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2447	S		[(S)-(((R)-4-Hydroxy-9-(dimethylamino)nonyl)thio)methyl-

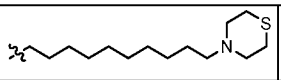
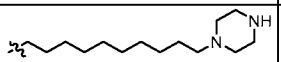
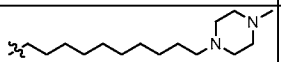
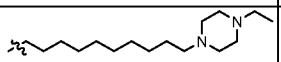
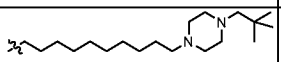
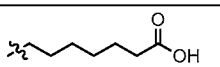
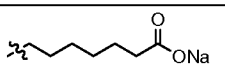
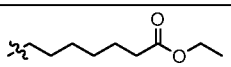
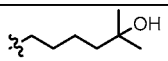
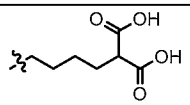
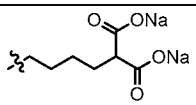
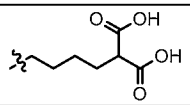
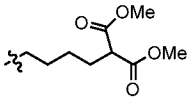
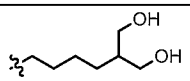
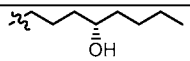
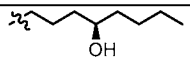
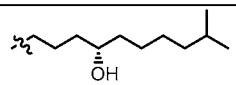
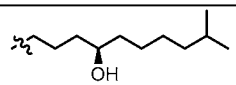
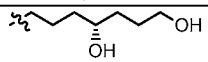
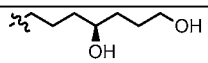
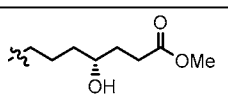
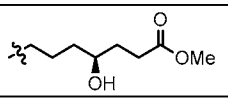
			Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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2449	S		[(S)-(((R)-4-Hydroxy-9-(diethylamino)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2450	S		[(S)-(((S)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2451	S		[(S)-(((R)-4-Hydroxy-9-(neopentylamino)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2452	S		[(S)-(((S)-4-Hydroxy-9-(imidazol-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2453	S		[(S)-(((R)-4-Hydroxy-9-(imidazo-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2454	S		[(S)-(((S)-4-Hydroxy-9-morpholinononyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2455	S		[(S)-(((R)-4-Hydroxy-9-morpholinononyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2456	S		[(S)-(((S)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2457	S		[(S)-(((R)-4-Hydroxy-9-thiomorpholinononyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2458	S		[(S)-(((S)-4-Hydroxy-9-piperazin-1-ylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2459	S		[(S)-(((R)-4-Hydroxy-9-piperazin-1-ylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2460	S		[(S)-(((S)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2461	S		[(S)-(((R)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2462	S		[(S)-(((S)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2463	S		[(S)-(((R)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2464	S		[(S)-(((R)-3-(Hydroxymethyl)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2465	S		[(S)-(((S)-3-(Hydroxymethyl)nonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2466	S		[(S)-(((R)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2467	S		[(S)-(((S)-3-(Hydroxymethyl)-9-methyldecyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2468	S		[(S)-(((R)-3-(Hydroxymethyl)-8-hydroxyhoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2469	S		[(S)-(((S)-3-(Hydroxymethyl)-8-hydroxyoctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

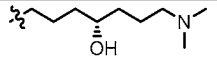
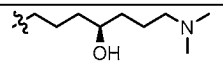
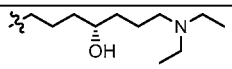
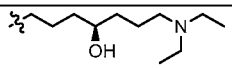
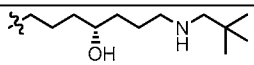
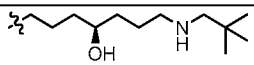
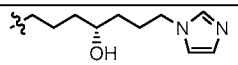
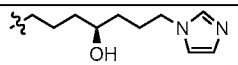
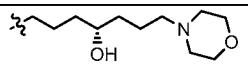
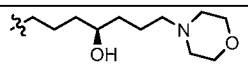
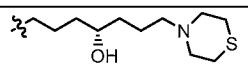
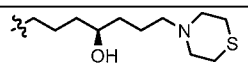
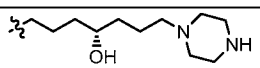
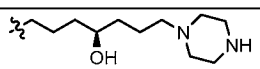
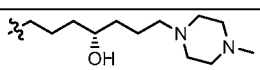
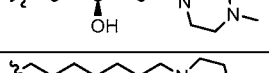
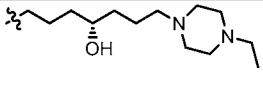
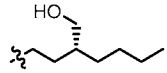
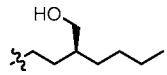
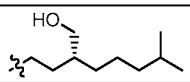
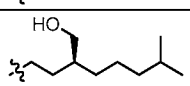
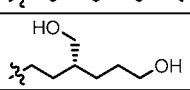
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2471	S		[(S)-(((S)-3-Hydroxy-8-methoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2472	S		[(S)-(((R)-3-Hydroxy-8-ethoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2473	S		[(S)-(((S)-3-Hydroxy-8-ethoxy-8-oxooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2474	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2475	S		[(S)-(((R)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2476	S		[(S)-(((S)-3-(Hydroxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2477	S		[(S)-(((R)-3-(Hydroxymethyl)-8-(diethylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2478	S		[(S)-(((R)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2479	S		[(S)-(((S)-3-Hydroxy-8-(neopentylamino)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2480	S		[(S)-(((R)-3-Hydroxymethyl-8-(imidazol-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2481	S		[(S)-(((S)-3-Hydroxymethyl-8-(imidazo-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2482	S		[(S)-(((R)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2483	S		[(S)-(((S)-3-Hydroxymethyl-8-morpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2484	S		[(S)-(((R)-3-Hydroxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2485	S		[(S)-(((S)-3-Hydroxymethyl-8-thiomorpholinooctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2486	S		[(S)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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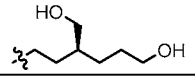
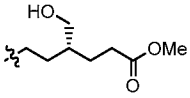
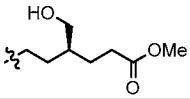
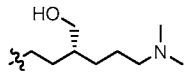
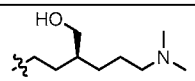
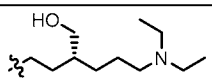
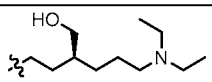
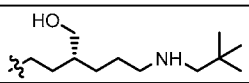
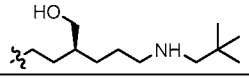
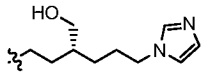
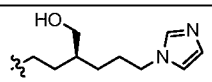
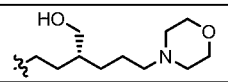
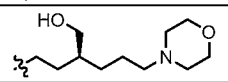
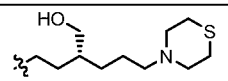
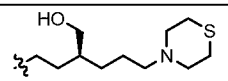
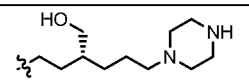
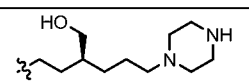
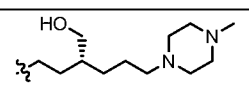
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2489	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2490	S		[(S)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2491	S		[(S)-(((S)-3-Hydroxymethyl-8-(4-isopropylpiperazin-1-yl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2492	S		[(S)-(((R)-2-(2-Hydroxyethyl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2493	S		[(S)-(((S)-2-(2-Hydroxyethyl)octyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2494	S		[(S)-(((R)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2495	S		[(S)-(((S)-2-(2-Hydroxyethyl)-8-methylnonyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2496	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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2498	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2499	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2500	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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2502	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2503	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2504	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

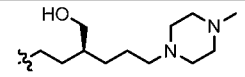
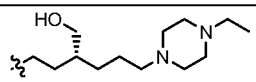
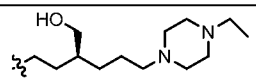
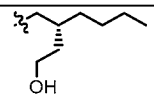
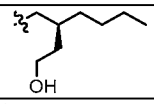
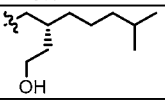
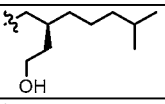
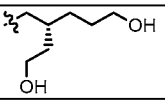
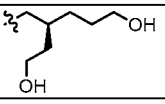
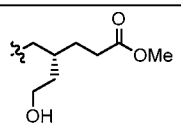
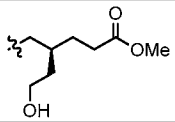
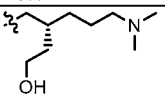
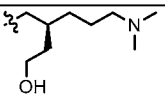
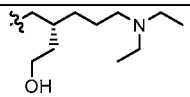
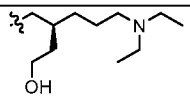
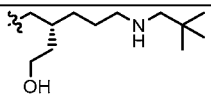
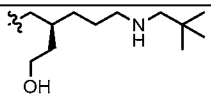
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2506	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2507	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2508	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2509	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2510	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2511	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2512	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2513	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-piperazin-1-ylheptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2514	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2515	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(4-methylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2516	S		[(S)-(((R)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2517	S		[(S)-(((S)-2-(2-Hydroxyethyl)-7-(4-ethylpiperazin-1-yl) heptyl)thio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2518	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2519	S		[(S)-(9-Carboxynonylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin-potassium salt
2520	S		[(S)-(9-(Ethoxycarbonyl)nonylthio)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2521	O		[(R)-(8-(N,N-Dimethylamino)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2522	O		[(R)-((N,N-Diethylamino)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

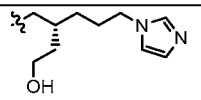
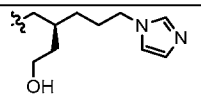
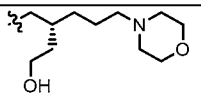
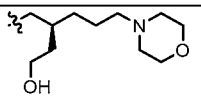
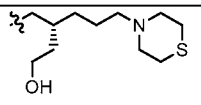
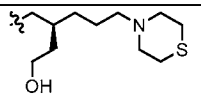
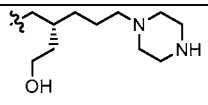
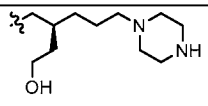
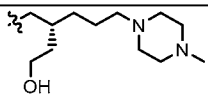
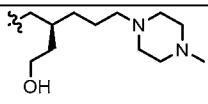
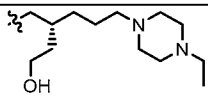
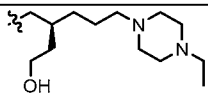
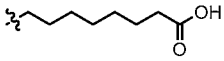
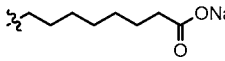
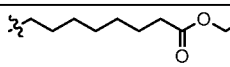
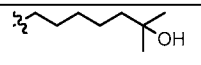
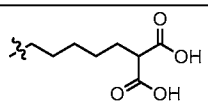
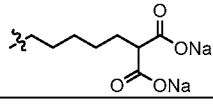
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2524	O		[(R)-(8-(Neopentylamino)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2525	O		[(R)-(8-(methyl(neopentyl)amino)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2526	O		[(R)-(8-(Ethyl(neopentyl)amino)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2527	O		[(R)-(8-(1H-imidazol-1-yl)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2528	O		[(R)-(8-(Pyrrolidin-1-yl)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2529	O		[(R)-(8-(Piperidin-1-yl)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2530	O		[(R)-((8-Morpholinooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2531	O		[(R)-((8-Thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2532	O		[(R)-((8-(Piperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2533	O		[(R)-((8-(4-Methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2534	O		[(R)-((8-(4-Ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2535	O		[(R)-((8-(4-Neopentylpiperazin-1-yl)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2536	O		[(R)-(10-(N,N-Dimethylamino)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2537	O		[(R)-(10-(N,N-Diethylamino)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2538	O		[(R)-(10-(N,N-Diisobutylamino)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2539	O		[(R)-(10-(Neopentylamino)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2540	O		[(R)-(10-(N-Methyl-N-neopentyl)amino)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2541	O		[(R)-(10-(N-Ethyl-N-neopentyl)amino)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2542	O		[(R)-(10-(1H-imidazol-1-yl)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2543	O		[(R)-(10-(Pyrrolidin-1-yl)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2544	O		[(R)-(10-(Piperidin-1-yl)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2545	O		[(R)-((10-Morpholinodecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

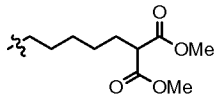
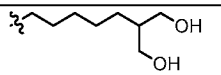
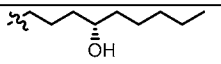
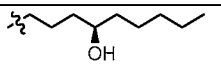
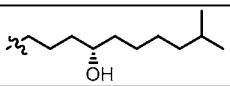
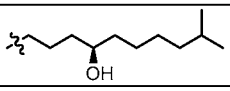
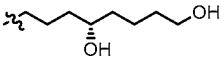
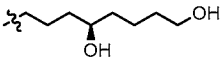
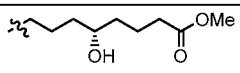
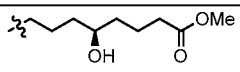
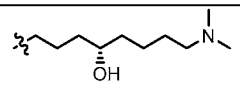
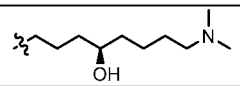
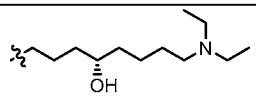
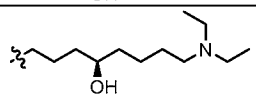
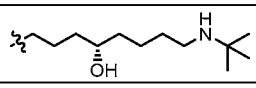
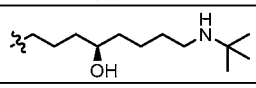
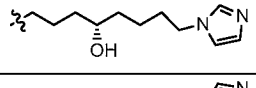
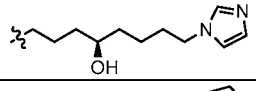
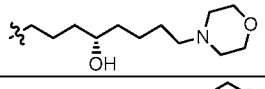
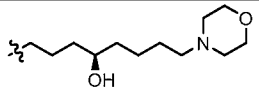
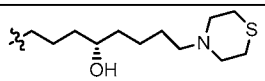
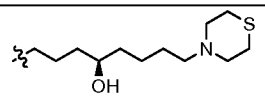
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2547	O		[(R)-((10-(piperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2548	O		[(R)-((10-(4-Methylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2549	O		[(R)-((10-(4-Ethylpiperazin-1-yl)decyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2550	O		[(R)-((10-(4-Neopentylpiperazin-1-yl)decyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2551	O		[(R)-(6-Carboxyhexyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2552	O		[(R)-(6-Carboxyhexyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin-sodium salt
2553	O		[(R)-(6-(Ethoxycarbonyl)hexyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2554	O		[(R)-((5-Hydroxy-5-methylhexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2555	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2556	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin- disodium salt
2557	O		[(R)-((5,5'-Dicarboxy)pentyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2558	O		[(R)-((6-Methoxy-5-(methoxycarbonyl)-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2559	O		[(R)-((6-Hydroxy-5-hydroxymethylhexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2560	O		[(R)-(((S)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2561	O		[(R)-((R)-(4-Hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2562	O		[(R)-((S)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2563	O		[(R)-((R)-4-Hydroxy-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2564	O		[(R)-((S)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2565	O		[(R)-((R)-4,7-Dihydroxyheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2566	O		[(R)-(((S)-4-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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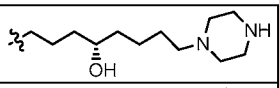
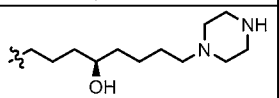
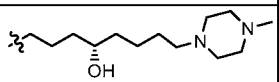
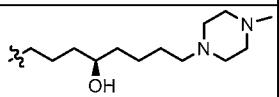
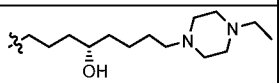
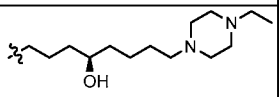
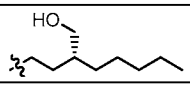
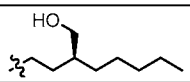
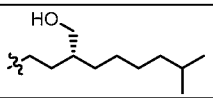
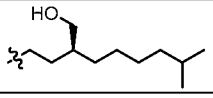
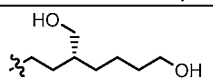
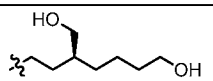
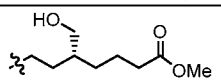
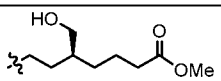
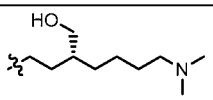
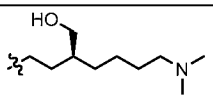
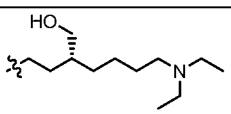
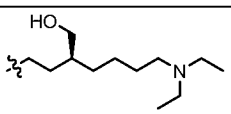
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2570	O		[(R)-(((S)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2571	O		[(R)-(((R)-4-Hydroxy-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2572	O		[(R)-(((S)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2573	O		[(R)-(((R)-4-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2574	O		[(R)-(((S)-4-Hydroxy-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2575	O		[(R)-(((R)-4-Hydroxy-7-(imidazo-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2576	O		[(R)-(((S)-4-Hydroxy-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2577	O		[(R)-(((R)-4-Hydroxy-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2578	O		[(R)-(((S)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2579	O		[(R)-(((R)-4-Hydroxy-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2580	O		[(R)-(((S)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2581	O		[(R)-(((R)-4-Hydroxy-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2582	O		[(R)-(((S)-4-Hydroxy-7-(4-methylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2583	O		[(R)-(((R)-4-Hydroxy-7-(4-methylpiperazin-1-yl)heptyl) oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2584	O		[(R)-(((S)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptylcyclos)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2585	O		[(R)-(((R)-4-Hydroxy-7-(4-ethylpiperazin-1-yl) heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2586	O		[(R)-(((R)-3-(Hydroxymethyl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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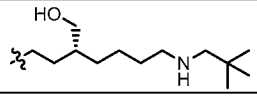
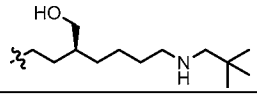
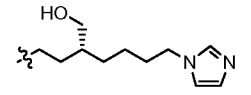
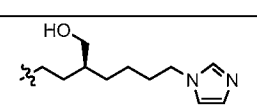
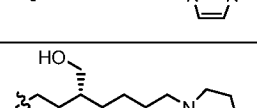
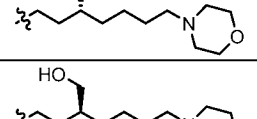
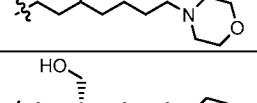
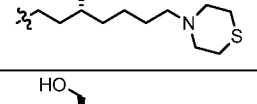
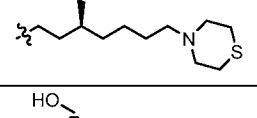
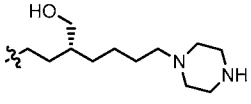
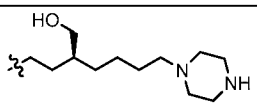
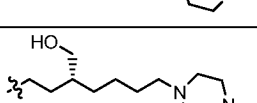
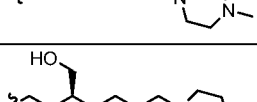
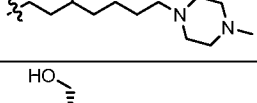
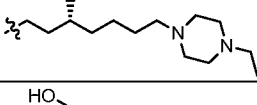
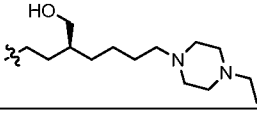
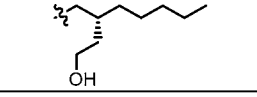
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2593	O		[(R)-(((S)-3-Hydroxy-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2594	O		[(R)-(((R)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2595	O		[(R)-(((S)-3-(Hydroxymethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2596	O		[(R)-(((R)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2597	O		[(R)-(((S)-3-(Hydroxymethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2598	O		[(R)-(((R)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2599	O		[(R)-(((S)-3-Hydroxy-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2600	O		[(R)-(((R)-3-Hydroxymethyl-6-(imidazol-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2601	O		[(R)-(((S)-3-Hydroxymethyl-6-(imidazo-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2602	O		[(R)-(((R)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2603	O		[(R)-(((S)-3-Hydroxymethyl-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2604	O		[(R)-(((R)-3-Hydroxymethyl-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2605	O		[(R)-(((S)-3-Hydroxymethyl-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2606	O		[(R)-(((R)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2607	O		[(R)-(((S)-3-Hydroxymethyl-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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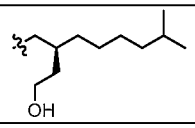
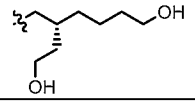
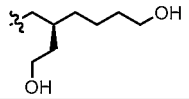
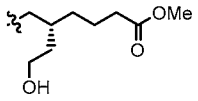
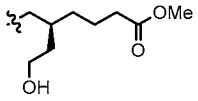
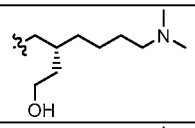
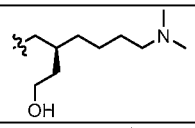
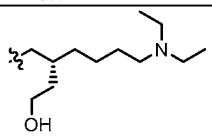
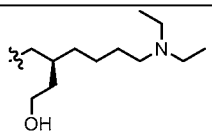
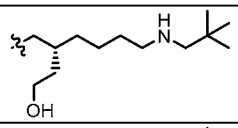
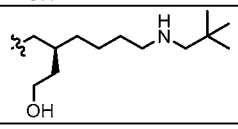
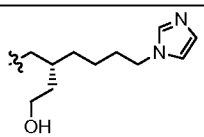
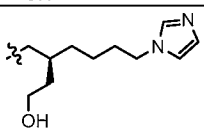
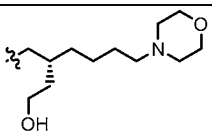
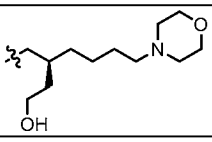
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2610	O		[(R)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2611	O		[(R)-(((S)-3-Hydroxymethyl-6-(4-isopropylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2612	O		[(R)-(((R)-2-(2-Hydroxyethyl)hexyl)oxy)methyl-Sar]-3-cyclosporin
2613	O		[(R)-(((S)-2-(2-Hydroxyethyl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2614	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2615	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2616	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2617	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-hydroxypentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2618	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2619	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-methoxy-5-oxopentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2620	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2621	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(dimethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2622	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2623	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(diethylamino)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2624	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(neopentylamino)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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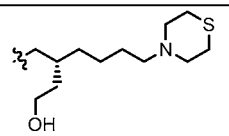
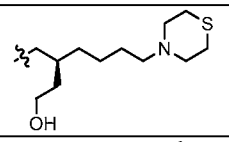
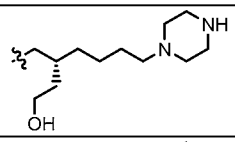
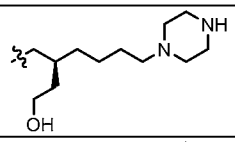
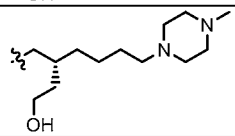
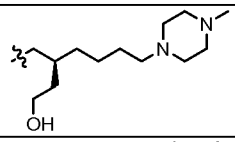
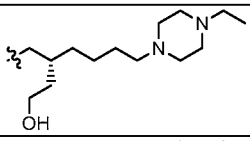
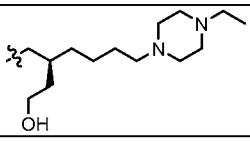
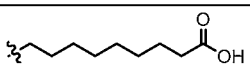
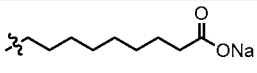
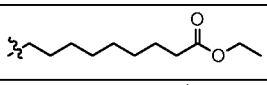
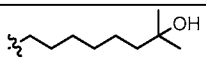
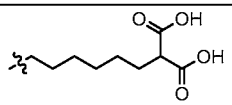
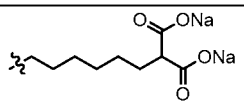
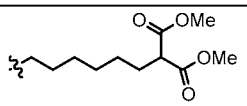
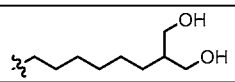
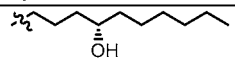
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2627	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(imidazol-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2628	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-morpholinopentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2629	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-morpholinopentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2630	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2631	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-thiomorpholinopentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2632	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2633	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-piperazin-1-ylpentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2634	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2635	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(4-methylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2636	O		[(R)-(((R)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2637	O		[(R)-(((S)-2-(2-Hydroxyethyl)-5-(4-ethylpiperazin-1-yl)pentyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2638	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2639	O		[(R)-(7-Carboxyheptyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin-sodium salt
2640	O		[(R)-(7-(Ethoxycarbonyl)heptyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2641	O		[(R)-((6-Hydroxy-6-methylheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2642	O		[(R)-((6,6'-Dicarboxy)hexyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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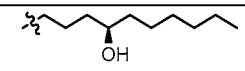
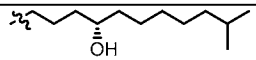
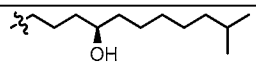
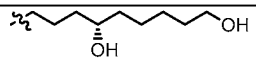
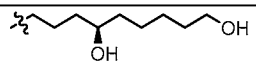
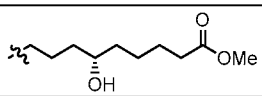
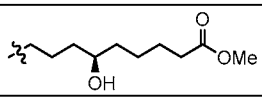
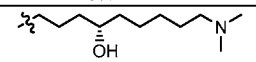
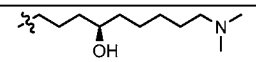
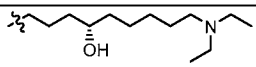
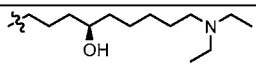
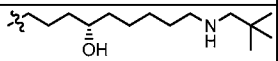
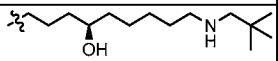
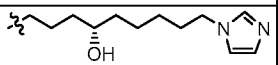
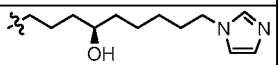
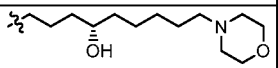
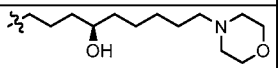
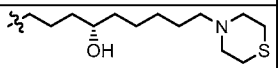
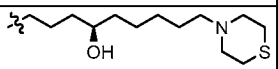
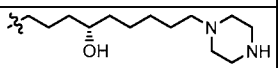
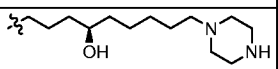
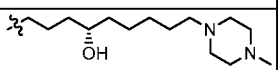
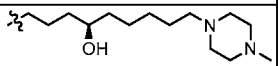
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2646	O		[(R)-((S)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2647	O		[(R)-((R)-(4-Hydroxynonyl)oxy)methyl-Sar]-3-cyclosporin
2648	O		[(R)-((S)-4-Hydroxy-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2649	O		[(R)-((R)-4-Hydroxy-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2650	O		[(R)-(((S)-4,8-Dihydroxyoctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2651	O		[(R)-(((R)-4,8-Dihydroxyoctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2652	O		[(R)-(((S)-4-Hydroxy-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2653	O		[(R)-(((R)-4-Hydroxy-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2654	O		[(R)-(((S)-4-Hydroxy-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2655	O		[(R)-(((R)-4-Hydroxy-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2656	O		[(R)-(((S)-4-Hydroxy-8-(diethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2657	O		[(R)-(((R)-4-Hydroxy-8-(diethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2658	O		[(R)-(((S)-4-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2659	O		[(R)-(((R)-4-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2660	O		[(R)-(((S)-4-Hydroxy-8-(imidazol-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2661	O		[(R)-(((R)-4-Hydroxy-8-(imidazo-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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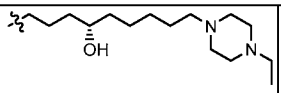
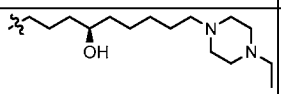
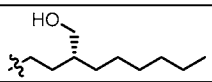
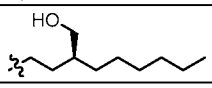
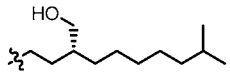
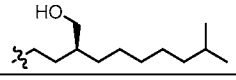
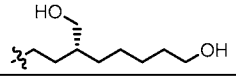
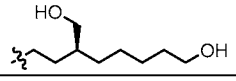
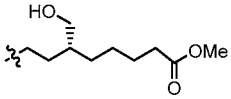
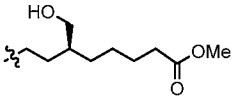
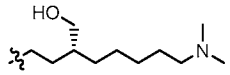
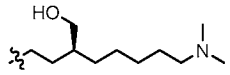
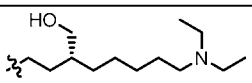
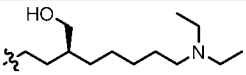
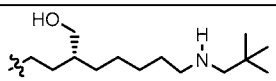
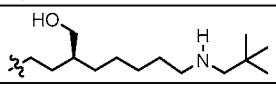
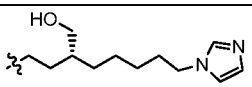
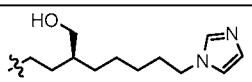
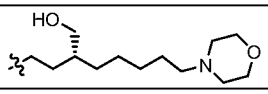
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2668	O		[(R)-(((S)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2669	O		[(R)-(((R)-4-Hydroxy-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2670	O		[(R)-(((S)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2671	O		[(R)-(((R)-4-Hydroxy-8-(4-ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2672	O		[(R)-(((R)-3-(Hydroxymethyl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2673	O		[(R)-(((S)-3-(Hydroxymethyl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2674	O		[(R)-(((R)-3-(Hydroxymethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2675	O		[(R)-(((S)-3-(Hydroxymethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2676	O		[(R)-((((R)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2677	O		[(R)-((((S)-3-(Hydroxymethyl)-7-hydroxyl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2678	O		[(R)-(((R)-3-Hydroxymethyl-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2679	O		[(R)-(((S)-3-Hydroxy-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2680	O		[(R)-((((R)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2681	O		[(R)-((((S)-3-(Hydroxymethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2682	O		[(R)-((((R)-3-(Hydroxymethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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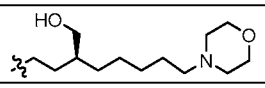
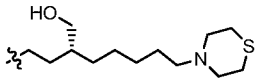
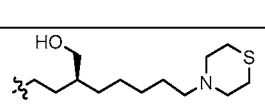
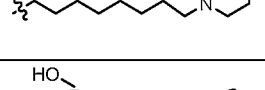
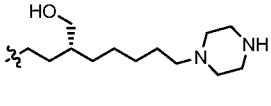
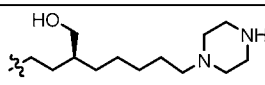
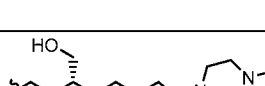
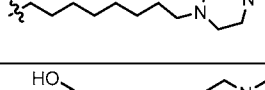
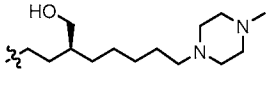
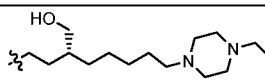
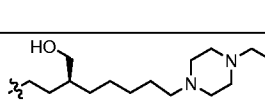
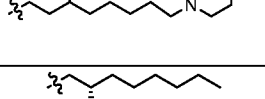
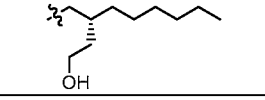
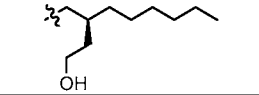
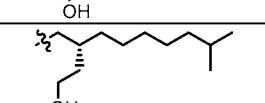
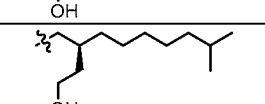
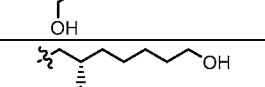
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2685	O		[(R)-(((S)-3-Hydroxy-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2686	O		[(R)-(((R)-3-Hydroxymethyl-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2687	O		[(R)-(((S)-3-Hydroxymethyl-7-(imidazo-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2688	O		[(R)-(((R)-3-Hydroxymethyl-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2689	O		[(R)-(((S)-3-Hydroxymethyl-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2690	O		[(R)-(((R)-3-Hydroxymethyl-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2691	O		[(R)-(((S)-3-Hydroxymethyl-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2692	O		[(R)-(((R)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2693	O		[(R)-(((S)-3-Hydroxymethyl-7-piperazin-1-ylheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2694	O		[(R)-(((R)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2695	O		[(R)-(((S)-3-Hydroxymethyl-7-(4-methylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2696	O		[(R)-(((R)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2697	O		[(R)-(((S)-3-Hydroxymethyl-7-(4-ethylpiperazin-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2698	O		[(R)-(((R)-2-(2-Hydroxyethyl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2699	O		[(R)-(((S)-2-(2-Hydroxyethyl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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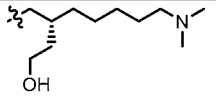
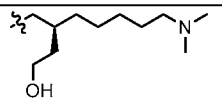
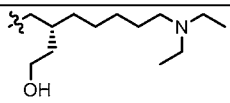
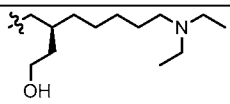
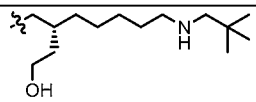
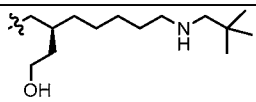
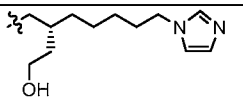
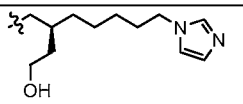
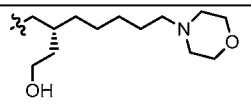
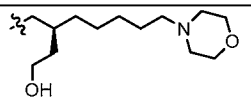
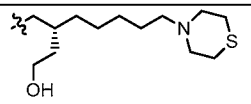
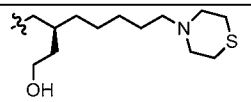
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2703	O		[(R)-((((S)-2-(2-Hydroxyethyl)-6-hydroxy)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2704	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2705	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-methoxy-6-oxohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2706	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2707	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(dimethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2708	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2709	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(diethylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2710	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(neopentylamino)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2711	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(neopentylamino)hepxyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2712	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(imidazol-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2713	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(imidazo-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2714	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2715	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-morpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

2716	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2717	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-thiomorpholinohexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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2719	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-piperazin-1-ylhexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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2721	O		[(R)-(((S)-2-(2-Hydroxyethyl)-6-(4-methylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2722	O		[(R)-(((R)-2-(2-Hydroxyethyl)-6-(4-ethylpiperazin-1-yl)hexyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
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2725	O		[(R)-(8-Carboxyoctyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin-potassium salt
2726	O		[(R)-(8-(Ethoxycarbonyl)octyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2727	O		[(R)-((7-Hydroxy-7-methyloctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2728	O		[(R)-((7,7'-Dicarboxy)heptyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2729	O		[(R)-((7,7'-Dicarboxy)heptyloxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin- disodium salt
2730	O		[(R)-((8-Methoxy-7-(methoxycarbonyl)-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2731	O		[(R)-((8-Hydroxy-7-hydroxymethyloctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2732	O		[(R)-(((S)-4-Hydroxydecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

2733	O		[(R)-(((R)-4-Hydroxydecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2734	O		[(R)-(((S)-4-Hydroxy-10-methylundecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2735	O		[(R)-(((R)-4-Hydroxy-10-methylundecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2736	O		[(R)-(((S)-4,9-Dihydroxynonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2737	O		[(R)-(((R)-4,9-Dihydroxynonyl)oxy)methyl-Sar]- -[(γ-allyloxy)-NMeLeu]-43-cyclosporin
2738	O		[(R)-(((S)-4-Hydroxy-9-methoxy-9-oxononyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2739	O		[(R)-(((R)-4-Hydroxy-9-methoxy-9-oxononyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2740	O		[(R)-(((S)-4-Hydroxy-9-(dimethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2741	O		[(R)-(((R)-4-Hydroxy-9-(dimethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2742	O		[(R)-(((S)-4-Hydroxy-9-(diethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2743	O		[(R)-(((R)-4-Hydroxy-9-(diethylamino)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2744	O		[(R)-(((S)-4-Hydroxy-9-(neopentylamino)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2745	O		[(R)-(((R)-4-Hydroxy-9-(neopentylamino)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2746	O		[(R)-(((S)-4-Hydroxy-9-(imidazol-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2747	O		[(R)-(((R)-4-Hydroxy-9-(imidazo-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2748	O		[(R)-(((S)-4-Hydroxy-9-morpholinononyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2749	O		[(R)-(((R)-4-Hydroxy-9-morpholinononyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2750	O		[(R)-(((S)-4-Hydroxy-9-thiomorpholinononyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2751	O		[(R)-(((R)-4-Hydroxy-9-thiomorpholinononyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2752	O		[(R)-(((S)-4-Hydroxy-9-piperazin-1-ylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2753	O		[(R)-(((R)-4-Hydroxy-9-piperazin-1-ylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2754	O		[(R)-(((S)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2755	O		[(R)-(((R)-4-Hydroxy-9-(4-methylpiperazin-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

2756	O		[(R)-(((S)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2757	O		[(R)-(((R)-4-Hydroxy-9-(4-ethylpiperazin-1-yl)nonyyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2758	O		[(R)-(((R)-3-(Hydroxymethyl)nontyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2759	O		[(R)-(((S)-3-(Hydroxymethyl)nonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2760	O		[(R)-(((R)-3-(Hydroxymethyl)-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2761	O		[(R)-(((S)-3-(Hydroxymethyl)-9-methyldecyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2762	O		[(R)-(((R)-3-(Hydroxymethyl)-8-hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2763	O		[(R)-(((S)-3-(Hydroxymethyl)-8-hydroxyoctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2764	O		[(R)-(((R)-3-Hydroxymethyl-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2765	O		[(R)-(((S)-3-Hydroxy-8-methoxy-8-oxooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2766	O		[(R)-(((S)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2767	O		[(R)-(((R)-3-(Hydroxymethyl)-8-(dimethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2768	O		[(R)-(((S)-3-(Hydroxymethyl)-8-(diethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2769	O		[(R)-(((R)-3-(Hydroxymethyl)-8-(diethylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2770	O		[(R)-(((R)-3-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2771	O		[(R)-(((S)-3-Hydroxy-8-(neopentylamino)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2772	O		[(R)-(((R)-3-Hydroxymethyl-8-(imidazol-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2773	O		[(R)-(((S)-3-Hydroxymethyl-8-(imidazo-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2774	O		[(R)-(((R)-3-Hydroxymethyl-8-morpholinooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

2775	O		[(R)-(((S)-3-Hydroxymethyl-8-morpholinooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2776	O		[(R)-(((R)-3-Hydroxymethyl-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2777	O		[(R)-(((S)-3-Hydroxymethyl-8-thiomorpholinooctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2778	O		[(R)-(((R)-3-Hydroxymethyl-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2779	O		[(R)-(((S)-3-Hydroxymethyl-8-piperazin-1-yloctyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2780	O		[(R)-(((R)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2781	O		[(R)-(((S)-3-Hydroxymethyl-8-(4-methylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2782	O		[(R)-(((R)-3-Hydroxymethyl-6-(4-ethylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2783	O		[(R)-(((S)-3-Hydroxymethyl-8-(4-isopropylpiperazin-1-yl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2784	O		[(R)-(((R)-2-(2-Hydroxyethyl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2785	O		[(R)-(((S)-2-(2-Hydroxyethyl)octyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2786	O		[(R)-(((R)-2-(2-Hydroxyethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2787	O		[(R)-(((S)-2-(2-Hydroxyethyl)-8-methylnonyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2788	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2789	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-hydroxyheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2790	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2791	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-methoxy-7-oxoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

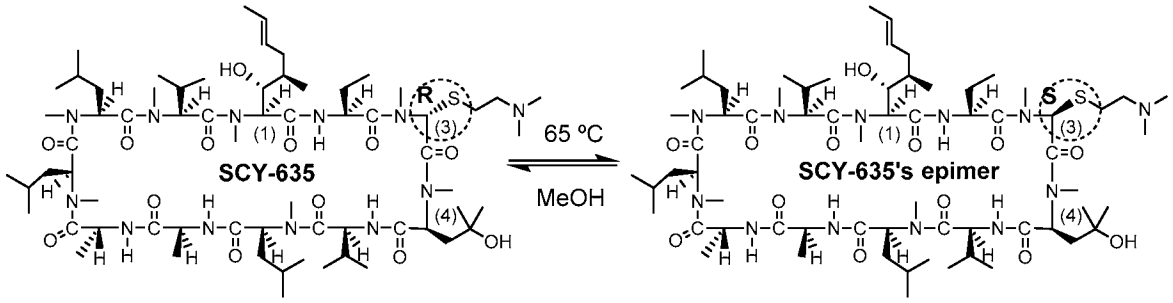
2792	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2793	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(dimethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2794	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2795	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(diethylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2796	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2797	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(neopentylamino)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2798	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2799	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-(imidazol-1-yl)heptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2800	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2801	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-morpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2802	O		[(R)-(((R)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin
2803	O		[(R)-(((S)-2-(2-Hydroxyethyl)-7-thiomorpholinoheptyl)oxy)methyl-Sar]-3-[(γ-allyloxy)-NMeLeu]-4-cyclosporin

Example 2804

Stability Testing of [(R)-3-(N,N-Dimethylamino)ethylthio-Sar]-3-[(γ-Hydroxy)-NMeLeu]-4-cyclosporin (SCY-635) and Cyclosporin Derivatives

[0388] Stability of Cyclosporin derivatives was evaluated in methanol at 65 °C and 50 °C, and HPLC was used to monitor possible isomerization of these compounds. It was found that SCY-635 is not stable and can easily convert to its corresponding epimer, which is expected to have low or no anti-viral activity.

Epimerization of SCY-635* in MeOH at 65 °C



HPLC RT: 14.60 min
The equilibrium endpoint: ~ 58%

HPLC RT: 15.01 min
The equilibrium endpoint: ~ 42%

Epimerization	SCY-635's epimer %				
	2 hours	4 hours	6 hours	8 hours	10 hours
SCY-635 ⇌ SCY-635's epimer	24%	35%	39%	41%	43%

*SCY-635 was prepared according to a method described by: Evans M, et al., 2003, *Bioorg. Med. Chem. Lett.,* 4, 4415-4419; Carry J, *et al.,* 2004, *Synlett.* 2, 316-320; or U.S. Pat. No. 5,994,299 (each of which is incorporated herein by reference).

Epimerization of SCY-635's epimer* in MeOH at 65 °C

Epimerization	SCY-635 %		
	3 hours	6 hours	10 hours
SCY-635's epimer ⇌ SCY-635	51%	58%	58%

[0389] * During the stability study, it was found that SCY-635 transformed into its epimer, which was separated as a pure compound. HPLC RT: 14.60 minutes (SCY-635) and: 15.01 minutes (its epimer) (C8 reverse phase column, 250 mm, acetonitrile/0.077% NH_4OAc in water, operation temperature: 64 °C; Detector: 210 nm).

[0390] When the epimer was treated with MeOH at 65 °C, it also was found that it partially transformed to SCY-635. At the endpoint of the equilibrium, this solution contained about 58% of SCY-635 and about 42% of epimer.

Table 5, Epimerization of [(R)-2-(N, N-dimethylamino)ethylthio-Sar]-3-cyclosporin in MeOH at 65 °C

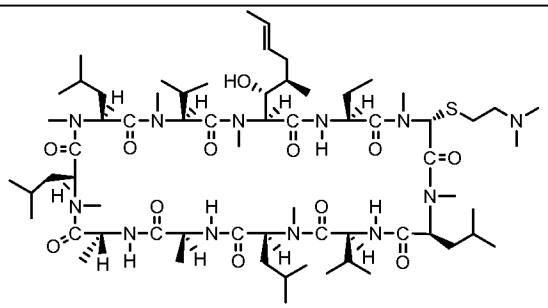
Compound	Epimerization%		
	2 hours	4 hours	6 hours
 [(R)-2-(N, N-Dimethylamino)ethylthio-Sar]-3-cyclosporin	~12%	~19%	~23%

Table 6, Epimerization of [(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin in MeOH at 65 °C

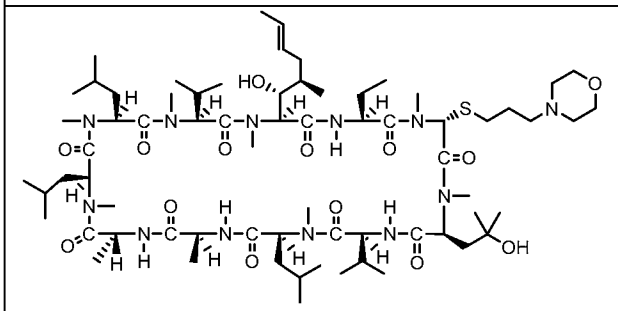
Compound	Epimerization% in MeOH at 65 °C				
	2 hours	4 hours	6 hours	8 hours	10 hours
 [(R)-3-(Morpholino)propylthio-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0%	0%	0%	Less than 1%	~10%

Table 7, Epimerization of [(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-Methoxy)-NMeLeu]-4-cyclosporin in MeOH at 65 °C

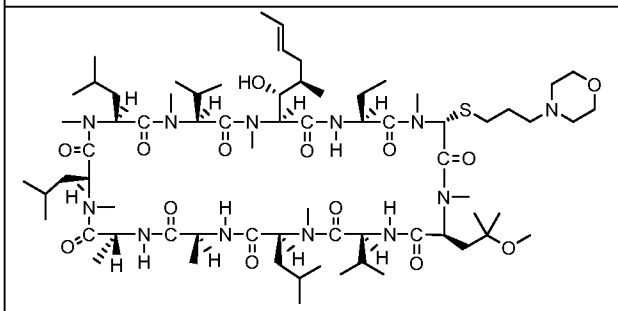
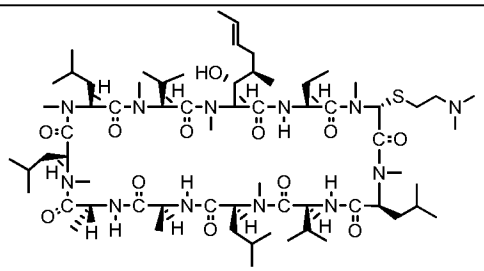
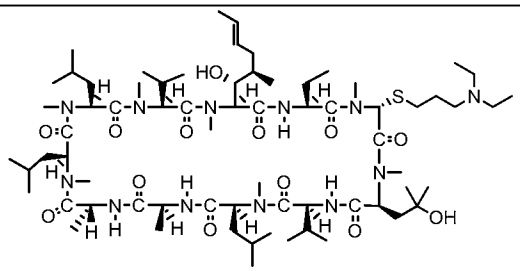
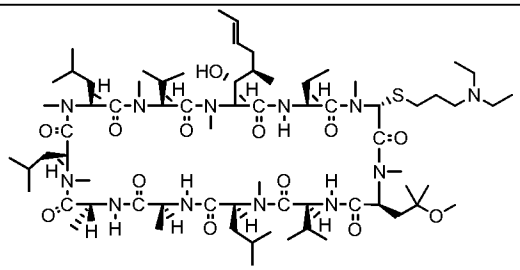
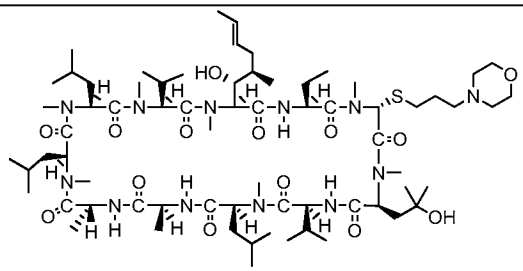
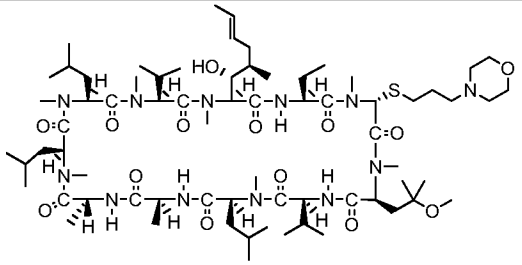
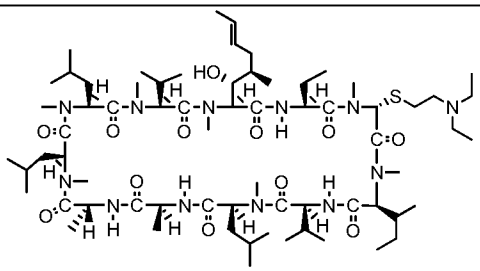
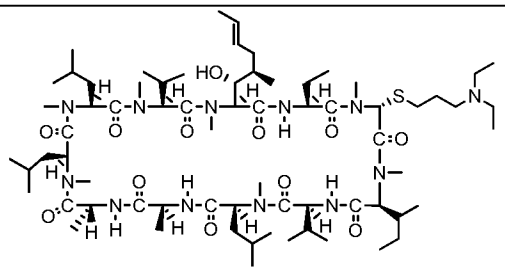
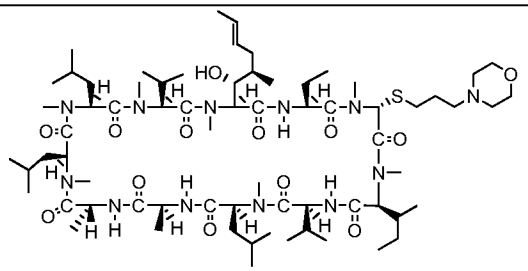
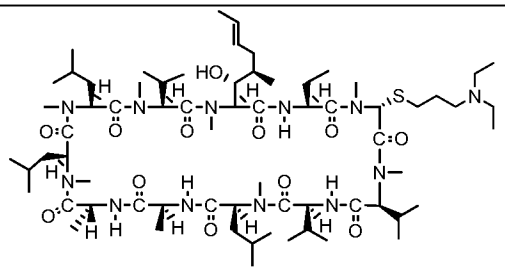
Compound	Epimerization% in MeOH at 65 °C					
	2 hours	4 hours	10 hours	22 hours	30 hours	38 hours
 [(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin	0%	0%	0%	0%	0%	0%

Table 8, Epimerization of Cyclosporin Derivatives in MeOH at 50 °C

Compounds	Epimerization%		
	29 hours	77 hours	125 hours
 [(R)-2-(N, N-Dimethylamino)ethylthio-Sar]-3-cyclosporin	~26%	~32%	~35%
 [(R)-3-(N, N Diethylamino)propylthio-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0%	Less than 1%	~12%
 [(R)-3-(N, N-Diethylamino)propylthio-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin	0%	0%	0%
 [(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0%	0%	0%

 [(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin	0%	0%	0%
 [(R)-2-(N,N-Diethylamino)ethylthio-Sar]-3-[NMeIle]-4-cyclosporin	~4%	~10%	~16%
 [(R)-3-(N,N-Diethylamino)propylthio-Sar]-3-[NMeIle]-4-cyclosporin	0%	0%	0%
 [(R)-3-(N-Morpholino)propylthio-Sar]-3-[NMeIle]-4-cyclosporin	0%	0%	0%
 [(R)-3-(N,N-Diethylamino)propylthio-Sar]-3-[N-MeVal]-4-cyclosporin	0%	0%	0%

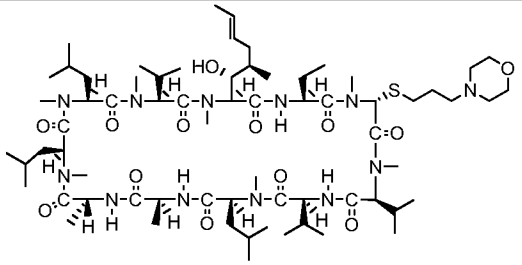
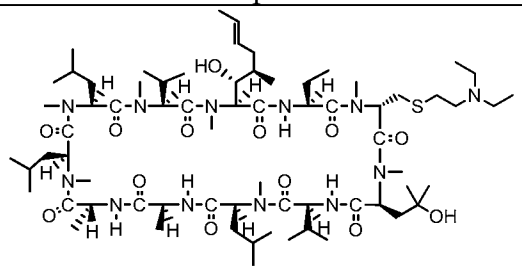
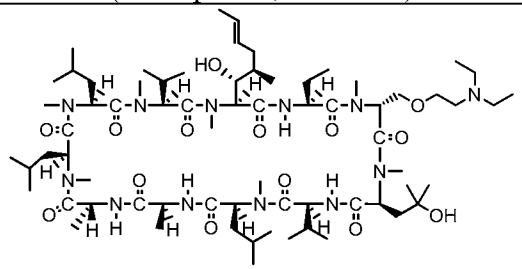
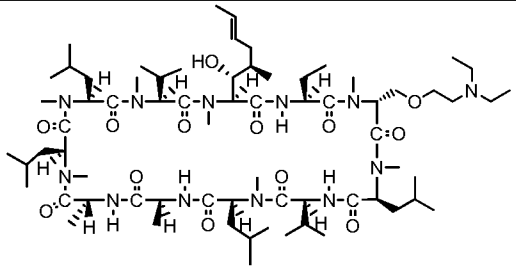
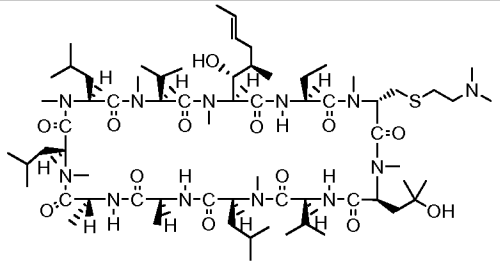
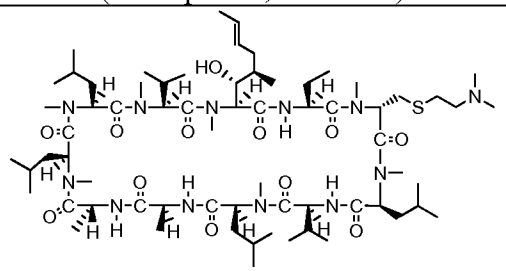
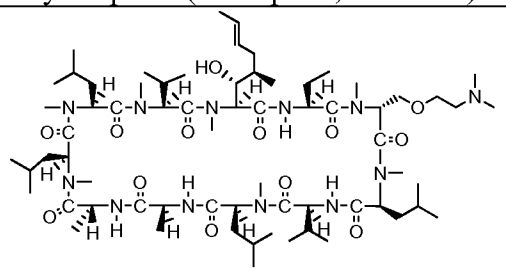
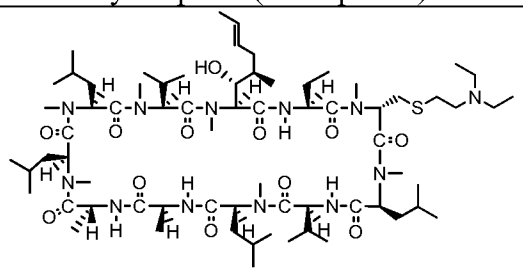
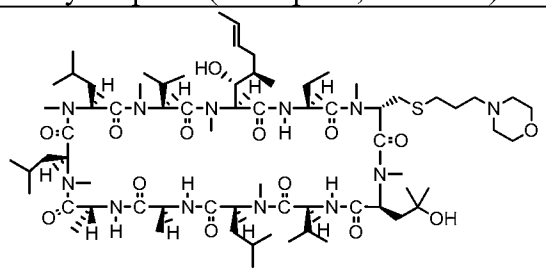
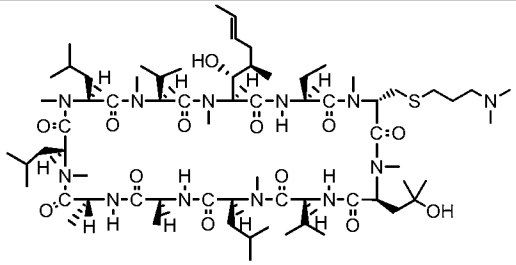
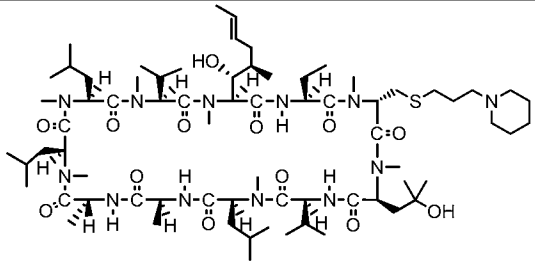
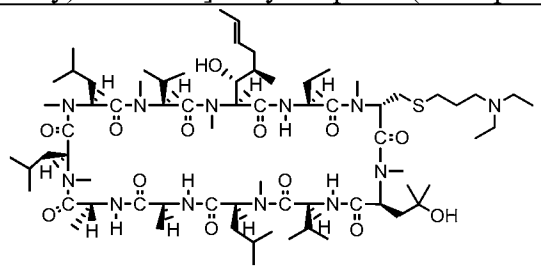
 [(R)-3-(N-Morpholino)propylthio-Sar]-3-[NMeVal]-4-cyclosporin	0%	0%	0%

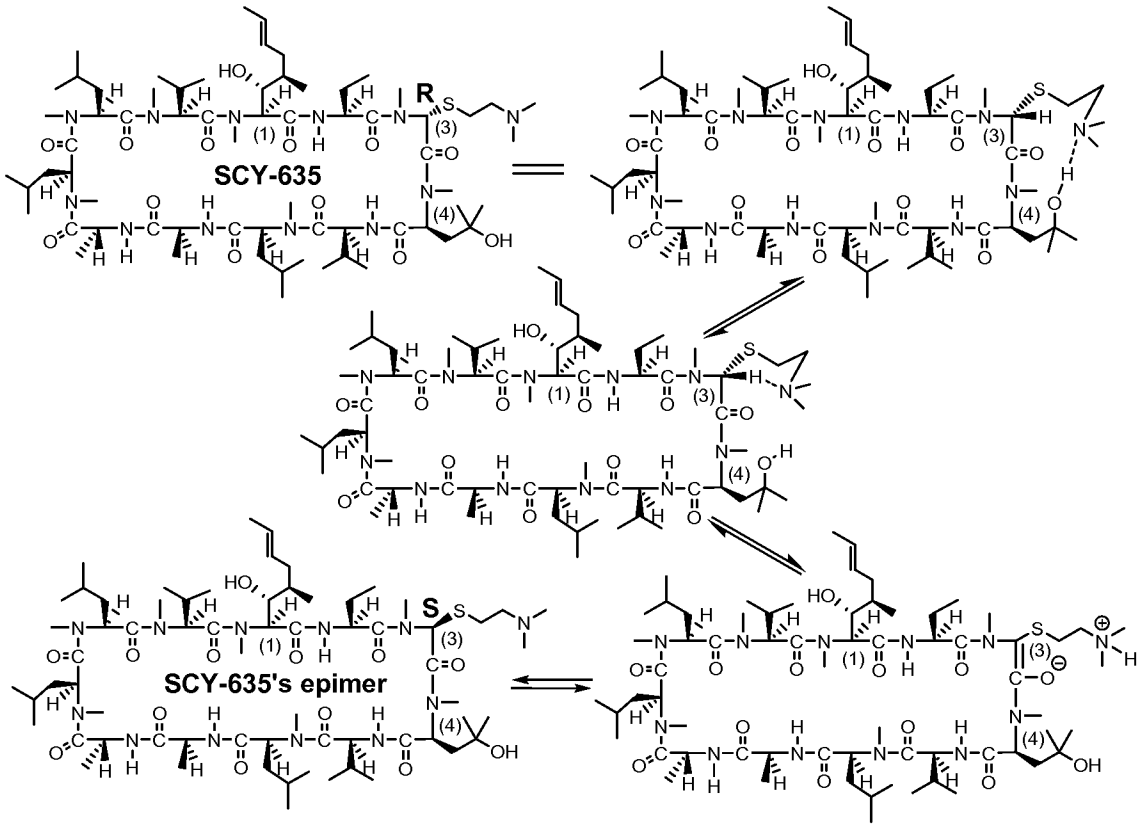
Table 9, Epimerization of Cyclosporin Derivatives in MeOH at 50 °C – 58 °C

Compound	Epimerization% after 168 hours
 [(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Example 32, isomer B)	0%
 [(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Example 105)	0%
 [(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-cyclosporin (Example 8)	0%

 [(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Example 31, isomer B)	0%
 [(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-cyclosporin (Example 6, isomer B)	0%
 [(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-cyclosporin (Example 14)	0%
 [(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-cyclosporin (Example 7, isomer B)	0%
 [(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Example 65))	0%

 [(S)-(3-(N,N-Dimethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Example 56)	0%
 [(S)-(3-(N-Piperidinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (Example 63)	0%
 [(S)-(3-(N,N-Diethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (Example 57)	0%

[0391] Based on the isomerization data, the inventors suggest that the epimerization of SCY-635 occurs through the following reaction machanism:



[0392] Thus, the two carbon side chain at position 3 of the sarcosine of cyclosporine contributes to the instability, because it can form a six-membered ring transition state, and stimulate the epimerization. Additionally, the epimerization is accelerated by the γ-hydroxyl group at the 4-position of leucine.

[0393] Accordingly, the inventors envisioned novel cyclosporine derivatives having enhanced stability while maintaining good cyclophilin binding activity. In particular, the inventors have surprisingly found that the masking the γ-hydroxyl group on leucine at position 4, elongating side carbon chain (*e.g.*, with 3 carbons or higher), and/or substituting the amine terminal at position 3 with a bulky side chain can prevent or minimize the epimerization. Specially, when the methylene substituents are introduced on position-3, those analogs are very stable, and can prevent the epimerization.

Example 2805

Anti HCV Activity of Cyclosporin Derivatives

[0394] Anti-HCV activity of cyclosporine derivatives were evaluated in the HCV subgenomic replicon assay. The assay use the cell line ET (luc-ubi-neo/ET), which is a Huh7 human hepatoma cell line harboring an HCV replicon with a stable luciferase (Luc)

reporter. HCV RNA replication was assessed by quantifying HCV replicon-derived luciferase activity. The antiviral activity of cyclosporine analogs were evaluated after drug treatment to derive EC_{50} and EC_{90} values by using the luciferase end point (Krieger, N., *et al.*, 2001, *J. Virol.* 75, 4614-4624; Pietschmann, T., *et al.*, 2002, *J. Virol.* 76, 4008-4021; each of which is incorporated herein by reference). Cytotoxicity was assessed in parallel.

Table 10, Testing results of certain representative compounds

Compound	Antiviral activity EC_{50} (μM)
Cyclosporine A	0.41
[N-MeIle]-4-cyclosporin (SDZ-NIM-811)	0.15
[N-MeVal]-4-cyclosporin (SDZ 220-384)	0.17
(R)-2-(N,N-Diethylamino)ethylthio-Sar]-3-[N-MeIle]-4-cyclosporin	0.04
(S)-2-(N,N-Diethylamino)ethylthio-Sar]-3-[N-MeIle]-4-cyclosporin	1.87
(R)-2-(N,N-Diethylamino)ethylthio-Sar]-3-[N-MeVal]-4-cyclosporin	0.04
(S)-2-(N,N-Diethylamino)ethylthio-Sar]-3-[N-MeVal]-4-cyclosporin	3.66
(R)-2-(N,N-Dimethylamino)ethylthio-Sar]-3-[N-MeVal]-4-cyclosporin	0.13
(R)-2-(N-neo-Pentylamino)ethylthio-Sar]-3-cyclosporin	0.23
(S)-2-(N-neo-Pentylamino)ethylthio-Sar]-3-cyclosporin	3.09
(R)-2-(N-iso-Butyl-N-iso-propylamino)ethylthio-Sar]-3-cyclosporin	0.48
(S)-2-(N-iso-Butyl-N-iso-propylamino)ethylthio-Sar]-3-cyclosporin	4.65
(R)-2-(N-Diethylamino)ethylthio-Sar]-3-cyclosporin	0.16
[(R)-2-(N,N-Diethylamino)ethylthio-Sar]-3-[(γ-Methylthio)methoxy-NMeLeu]-4-cyclosporin	0.11

Table 11, Testing results of certain representative compounds

Compound	Antiviral activity EC_{50} (μM)
[N-MeVal]-4-cyclosporin (SDZ 220-384)	0.12
(R)-2-(N,N-Dimethylamino)ethylthio-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (SCY-635)	0.08
[(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-dihydrocyclosporin	0.15
[(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.06
(R)-3-(N,N-Diethylamino)propylthio-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.07
[(R)-(3-(N-Morpholino)propylthio-Sar]-3-[(γ-ethoxy)methoxy-N-MeLeu]-4-cyclosporin	0.16
[(R)-2-(N,N-Diethylamino)ethylthio-Sar]-3-[(γ-methylthio)methoxy-N-MeLeu]-4-cyclosporin	0.13
[(R)-(3-(N-Morpholino)propylthio-Sar]-3-[(γ-methylthio)methoxy-N-MeLeu]-4-cyclosporin	0.16
[(R)-(3-(N-Morpholino)propylthio-Sar]-3-[(γ-benzyloxy)-N-MeLeu]-4-	0.28

cyclosporin	
[(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-(4-Methoxy)-benzyloxy)-N-MeLeu]-4-cyclosporin	0.28
[(R)-3-(N-Morpholino)propylthio-Sar]-3-[(γ-allyloxy)-N-MeLeu]-4-cyclosporin	0.15
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (isomer B)	0.03
[(R)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-Hydroxy)-N-MeLeu]-4-cyclosporin (isomer A)	2.12
[(γ-Methoxy)-N-MeLeu]-4-cyclosporin	0.18
[(γ-Methoxy)-N-MeLeu]-4-dihydrocyclosporin	0.35
[(γ-Methylthio)methoxy-N-MeLeu]-4-cyclospori	0.40
[γ -(2-Hydroxyethoxy)-N-MeLeu]-4-dihydrocyclosporin	0.43
[N-MeSer]-4-cyclosporin	0.56

Table 12, Testing results of certain representative compounds

Compound	Antiviral activity EC_{50} (μM)
[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[γ-(Hydroxy)-N-MeLeu]-4-cyclosporin (isomer B)	0.05
[(R)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[γ-(Hydroxy)-N-MeLeu]-4-cyclosporin (isomer A)	2.12
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin (isomer B)	0.03
[(S)-(2-(N-Morpholino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.02
[(S)-(2-(N-Piperidinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.04
[(S)-(2-(4-Methyl-N-piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.03
[(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.02
[(S)-(3-(N,N-Dimethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.05
[(S)-(3-(N,N-Diethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.03
[(S)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.05
[(S)-(2-(N-Isopropyl-N-methylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.04
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[(γ-methoxy)-NMeLeu]-4-cyclosporin	0.02
[(R)-(3-(N-Morpholino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.04
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-Methylthio)methoxy-NMeLeu]-4-cyclosporin	0.02
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-Ethoxy)methoxy-NMeLeu]-4-cyclosporin	0.02

[(R)-(3-(N-Pyrrolidinyl)propoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.12

Table 13, Testing results of certain representative compounds

Compound	Antiviral activity EC_{50} (μM)
[N-MeIle]-4-cyclosporin (SDZ-NIM-811)	0.14
[N-MeVal]-4-cyclosporin (SDZ 220-384)	0.14
[(R)-2-(N,N-Dimethylamino)ethylthio-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (SCY-635)	0.12
[D-N-MeAla]-3-[N-EtVal]-4-cyclosporin (Debio-025)	0.07
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (isomer B)	0.09
(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[γ-(Hydroxy)-N-MeLeu]-4-cyclosporin (isomer B)	0.13
[(S)-(2-(N-Morpholino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.06
[(S)-(3-(N-Piperidinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(2-(N-Piperidino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.08
[(S)-(2-(4-Methylpiperazino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.09
[(S)-(2-(N-Pyrrolidinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.11
[(S)-(3-(N-Pyrrolidinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.10
[(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(3-(4-Methyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.09
[(S)-(3-(N,N-Dimethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.11
[(S)-(3-(N,N-Diethylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.08
[(S)-(3-(N-Ethyl-N-isopropylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.06
[(S)-(2-(N-Ethyl-N-isopropylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.07
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.12
[(S)-(2-(N-Methyl-N-iso-propylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.10
[(S)-(2-(N-Isopropylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.19
[(S)-(2-(N,N-Diisobutylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.12
[(S)-(2-(N-Neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-	0.06

MeLeu]-4-cyclosporin	
[(S)-(2-(N-Ethyl-N-neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.06
[(S)-(2-(N-Methyl-N-neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.07
[(R)-(Ethoxycarbonylmethoxy)methyl-Sar]-3-cyclosporin	0.18
[(R)-(3-(N, N-Diethylamino)propoxy)methyl-Sar]-3-cyclosporin	0.12
[(R)-(3-(N,N-Dimethylamino)propoxy)methyl-Sar]-3-cyclosporin	0.13
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.06
[(R)-(3-(N-Morpholino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.09
[(R)-3-(N,N-Diethylamino)propylthio-Sar]-3-[N-MeIle]-4-cyclosporin	0.08
[(R)-(3-(N-Pyrrolidinyl)propoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.22
[(R)-3-(N,N-Diethylamino)propylthio-Sar]-3-[N-MeVal]-4-cyclosporin	0.07
[(R)-(3-(N-Morpholino)propylthio-Sar]-3-[N-MeVal]-4-cyclosporin	0.11
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[N-MeVal]-4-cyclosporin	0.14
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[N-MeIle]-4-cyclosporin	0.10
[(R)-(2-(N,N-Diethylamino)ethoxy)methyl-Sar]-3-[N-MeIle]-4-cyclosporin	0.16
[(R)-(3-(N-Piperidinyl)propoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.15
[(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-cyclosporin	0.15
[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-cyclosporin (isomer B)	0.17
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-cyclosporin (isomer B)	0.16
[(R)-(2-(N-Piperidinyl)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.14
[(R)-(2-(N-Pyrrolidino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.20
[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.10
[(S)-(3-(N,N-Dimethylamino)propylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.09
[(S)-(3-(N,N-Diethylamino)propylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.07
[(S)-(2-(N,N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.09
[(S)-(2-(N-Pyrrolidinyl)ethylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.09
[(S)-(2-(N-Morpholino)ethylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.11
[(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.15
[(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-methoxy)-N-	0.10

MeLeu]-4-cyclosporin	
[(R)-(3-(N,N-Diethylamino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.18
[(S)-(3-(N-Pyrrolidinyl)propylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.10
[(S)-[(3-(N-piperidino)propylthio)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.06
[(R)-(2-(N,N-Dimethylamino)ethoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.24
[(R)-(3-(N,N-Dimethylamino)propoxy)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.26
[(R)-(3-(N,N-Diethylamino)propoxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporine	0.10
[(R)-(2-(N-Morpholino)ethoxy)methyl-Sar]-3-[(γ-methoxy)-N-MeLeu]-4-cyclosporin	0.15

Table 14, Testing results of certain representative compounds

Compound	Antiviral activity EC_{50} (μM)
[(R)-2-(N,N-Dimethylamino)ethylthio-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (SCY-635)	0.11
[D-N-MeAla]-3-[N-EtVal]-4-cyclosporin (Debio-025)	0.05
[(S)-(2-(N-Neopentylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(2-(4-Ethyl-N-piperazinyl)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.06
[(S)-(3-(N,N-Diisobutylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.04
[(S)-(3-(N-Neopentylamino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(3-(N-Morpholino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.04
[(S)-(3-(N-Thiomorpholino)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(3-(4-Methyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.04
[(S)-(3-(4-Ethyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(3-(4-N-n-Propyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(3-(4-N-Isopropyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(3-(4-N-Isobutyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05
[(S)-(3-(4-N-Neopentyl-N-piperazinyl)propylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.06
[(S)-(4-(N,N-Diethylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.07

[(S)-(4-(N,N-Diisobutylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.04
[(S)-(4-(N-Neopentylamino)butylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.04
[(S)-(4-hydroxylbutylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.02
[(S)-(4-(2-(Diethylamino)ethoxy)butylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.05

Table 15, Testing results of certain representative compounds

Compound	Antiviral activity EC_{50} (μM)
[(R)-2-(N,N-Dimethylamino)ethylthio-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin (SCY-635)	0.14
[D-N-MeAla]-3-[N-EtVal]-4-cyclosporin (Debio-025)	0.05
[(S)-((3-(R)-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.07
[(S)-((3-(S)-(Hydroxymethyl)hexyl)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.07
[(S)-((*E*-4-Diethylamino-2-propyl-2-butene)thio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.06
[(S)-((5-Hydroxy-5-methyl)hexylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	0.06
[(S)-(6-Hydroxy-(5-hydroxymethyl)hexylthiomethyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	0.07

Example 2806

Anti HIV Activity of Cyclosporin Derivatives

[0395] Anti-HIV activity of cyclosporine derivatives were evaluated by cytoprotection assay in an acute infection model using CEM-SS cells and either HIV-1_{IIIB} or HIV-1 RF. Antiviral activity was determined as a reduction in virus-caused cytopathic effects when compounds prevent virus replication. Cytoprotection and compound cytotoxicity were evaluated using the tetrazollium dye MTS (Promega) to calculate cell viability following virus infection after 6-day incubation (Zhou G., et al., 2011, *J. Med. Chem.* 27, 7220-31; which is incorporated herein by reference).

Table 16, Testing results of certain representative compounds against HIV-1IIIB in CEM-SS cells (MTS Endpoint)

Compound	Antiviral activity EC_{50} (nM)
AZT	9.0
[(S)-(2-(N,N-Dimethylamino)ethylthio)methyl-Sar]-3-[(γ-Hydroxy)-NMeLeu]-4-cyclosporin (isomer B)	118.0

[(S)-(2-(N-Morpholino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-NMeLeu]-4-cyclosporin	94.9

Example 2807

Inhibition of Mitochondrial Permeability Transition (MPT)

[0396] The effect of cyclosporine analogs on mitochondrial permeability transition (MPT) was determined by a modified mitochondrial swelling assay measured as an influx of Ca^{2+}, published by J. Blattner *et al*., 2001, *Analytical Biochem*, 295, 220-226. Briefly, rat neuronal mitochondria in an ice-cold sucrose buffer were obtained after rat whole-body perfusion and a series of centrifugation. The total protein concentration in each sample batch was determined for standardization between assays. The mitochondrial swelling was induced by 100 micromolar of Calcium Chloride. Each compound (100 nM) was added to mitochondria 5 minutes before the addition of $Ca.^{2+}$. The value of absorbance at the certain wavelength (620nm) reflected the degree of mitochondrial swelling. The percentage of the swelling was calculated by comparing the absorbance in the present or absent compound of the interests.

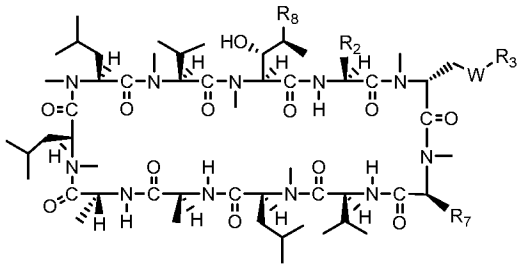
Table 17, Inhibition of Mitochondrial Swelling

Compounds	Mitochondrial Swelling Relative %
Control	100
Cyclosporin A	68.7
[(R)-2-(N-Diethylamino)ethylthio-Sar]-3-[(γ-methylthio)methoxy-N-MeLeu]-4-cyclosporin	52.4
[(S)-(2-(N-Diethylamino)ethylthio)methyl-Sar]-3-[(γ-hydroxy)-N-MeLeu]-4-cyclosporin	55.7

[0397] In above assay, the results in mitochondrial swelling strongly indicate that cyclosporine analogs can penetrate the mitochondrial membrane and inhibit mitochondrial swelling.

WE CLAIM:

1. A compound of Formula (I):



(I)

or pharmaceutically acceptable salt thereof, wherein:

R_8 is n-butyl, (*E*)-but-2-enyl,  , $-(CH_2)_4-SR_9$, $-(CH_2)_4-(C=O)OR_9$, or $-(CH_2)_3-(C=O)OR_9$;

each occurrence of R_9 is independently hydrogen or (C_1-C_6)alkyl;

R_2 is ethyl, 1-hydroxyethyl, isopropyl or n-propyl;

W is O, CH_2, NR_1, or S;

R_1 is hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1-C_6)$alkyl, $-C(=O)O(C_1-C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

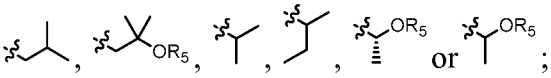
or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of (C_1-C_6)alkyl, phenyl and benzyl;

R_3 is:

$(C_7\text{-}C_{12})$alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

$(C_7\text{-}C_{12})$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino; or

$(C_7\text{-}C_{12})$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

R_7 is  ;

R_5 is:

H;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

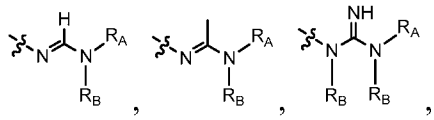
$(C_2\text{-}C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from hydroxy, $(C_1\text{-}C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2\text{-}C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3\text{-}C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, $(C_3\text{-}C_7)$cycloalkyl, aryl, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1\text{-}C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$,

$-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1\text{-}C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

p is an integer of 0, 1, 2, 3, 4, or 5; and

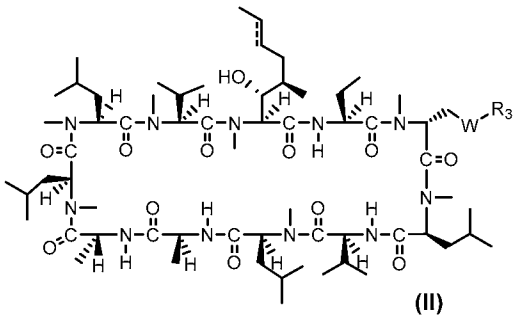
m is an integer of 1, 2, 3, 4 or 5.

2. The compound of claim 1, wherein R_8 is n-butyl.

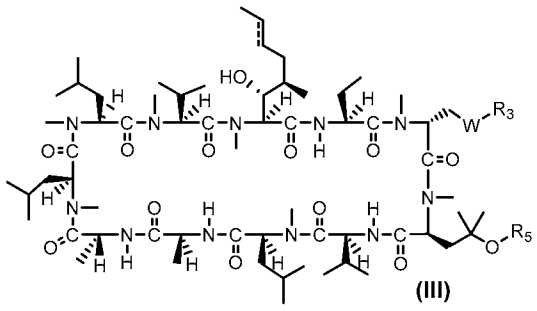
3. The compound of claim 1, wherein R_8 is (*E*)-but-2-enyl.

4. The compound of any one of claims 1-3, wherein R_2 is ethyl.

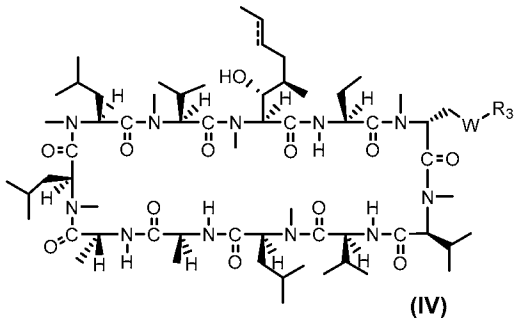
5. A compound of claim 1, having the structure of Formulae (II) through (V):



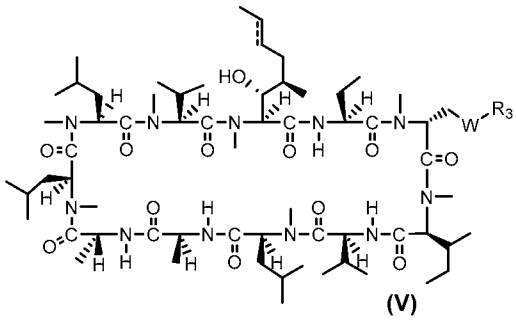
(II)



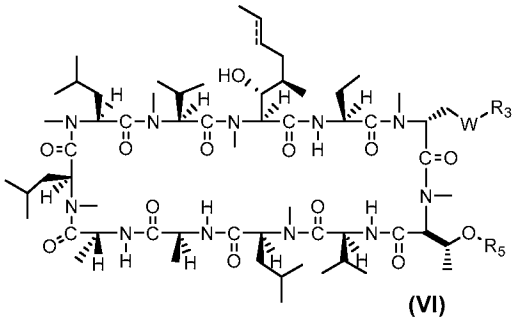
(III)



(IV)



(V)



(VI)

,

or pharmaceutically acceptable salt thereof, wherein:

represents a single bond or double bond;

each W is independently O, S, CH_2,or NR_1;

each R_1 is independently hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O(C_1-C_6)alkyl, -C(=O)O(C_1-C_6)alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of (C_1-C_6)alkyl, phenyl and benzyl;

each R_3 is independently:

(C_7-C_{12})alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

(C_7-C_{12})alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, (C_1-C_6)alkyl, aryl, $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$; or

(C_7-C_{12})alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

each R_5 is independently:

H;

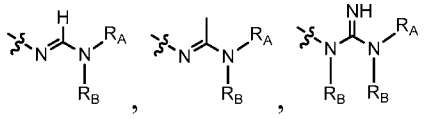
(C_1-C_6)alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2$-$C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, aryl, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $-NR_CCH_2(CH_2)_pNR_AR_B$,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, $(C_3$-$C_7)$cycloalkyl, aryl, $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

(C_1-C_6)alkyl, optionally substituted by one or more groups R_D which may be the same or different;

(C_2-C_6)alkenyl or (C_2-C_6)alkynyl;

(C_3-C_7)cycloalkyl optionally substituted with (C_1-C_6)alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O(C_1-C_6)alkyl, -C(=O)O(C_1-C_6)alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

or R_A and R_B, together with the nitrogen atom to which they are attached, form -N=CH-$NR_FR_{F'}$, -N=CMe-$NR_FR_{F'}$, or -$NR_FC(=NH)NR_FR_{F'}$;

each occurrence of R_C is independently hydrogen or (C_1-C_6)alkyl;

each occurrence of R_D is independently halogen, hydroxy, O(C_1-C_4)alkyl, C(=O)(C_1-C_4)alkyl, C(=O)O(C_1-C_4)alkyl;

each occurrence of R_F and $R_{F'}$ is independently hydrogen, (C_1-C_6)alkyl, phenyl, benzyl, or R_F and $R_{F'}$, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

p is an integer of 0, 1, 2, 3, 4, 5, or 6;

m is an integer of 1, 2, 3, 4, 5, or 6; and

n is an integer of 1, 2, 3, 4, 5 or 6.

6. The compound of any one of claims 1-5, wherein W is O.

7. The compound of any one of claims 1-5, wherein W is S.

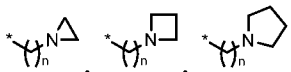
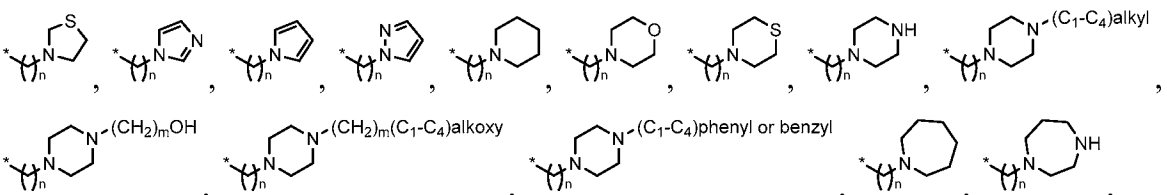
8. The compound of any one of claims 1-5, wherein W is NR_1.

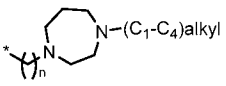
9. The compound of any one of claims 1-5, wherein W is NH.

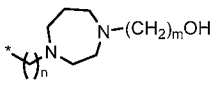
10. The compound of any one of claims 1-5, wherein W is $N(C_1\text{-}C_4)$alkyl.

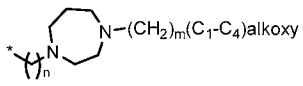
11. The compound of any one of claims 1-10, wherein R_3 is $-(CH_2)_nNR_AR_B$, wherein n is an integer of 7, 8, 9, 10, 11 or 12; and wherein each occurrence of R_A and R_B is independently hydrogen; $(C_1\text{-}C_4)$alkyl, optionally substituted by one or more groups R_D which may be the same or different, in which each occurrence of R_D is independently halogen, hydroxy, $O(C_1\text{-}C_4)$alkyl, $C(=O)(C_1\text{-}C_4)$alkyl, $C(=O)O(C_1\text{-}C_4)$alkyl; or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from $(C_1\text{-}C_4)$alkyl, phenyl and benzyl.

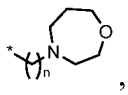
12. The compound of any one of claims 1-10, wherein R_3 is $-(CH_2)_nNR_AR_B$, wherein n is an integer of 7, 8, 9, 10, 11 or 12; and wherein R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from $(C_1\text{-}C_4)$alkyl, phenyl and benzyl.

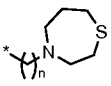
13. The compound of any one of claims 1-10, wherein R_3 is:  , 



,


,


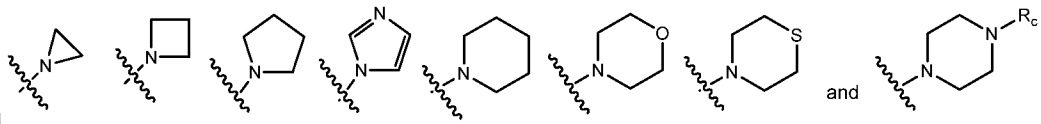
,


, or


, in which n is an integer of 7, 8, 9, 10, 11 or 12, and m is an integer of 2, 3, or 4.

14. The compound of any one of claims 1-13, wherein R_5 is H, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1$-$C_6)$alky, CH_2-O-$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)OR_A$, $(C_1$-$C_6)$-monoalkyl amine, $(C_1$-$C_6)$-dialkyl amine, or $(C_1$-$C_6)$-cyclic amine, in which said phenyl or benzyl is optionally substituted by one to three substitutents selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, and halogen; and R_A is H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkyl$O(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl; p is an integer of 0, 1, 2, 3, 4, or 5; and m is an integer of 1, 2, 3, 4 or 5.

15. The compound of any one of claims 1-14, wherein each occurrence R_A and R_B is independently H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, or $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkyl$O(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl.

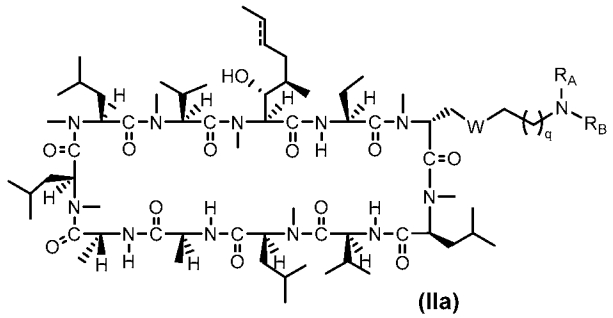
16. The compound of any one of claims 1-14, wherein R_A and R_B, together with the nitrogen atom to which they are attached, form a heterocycle selected from


, in which R_C is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph, CH_2CH_2OH, or $CH_2CH_2O(C_1$-$C_4)$alkyl.

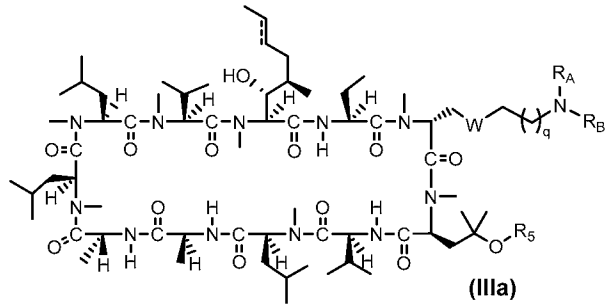
17. The compound of any one of claims 5-16, wherein represents a single bond.

18. The compound of any one of claims 5-16, wherein represents a double bond.

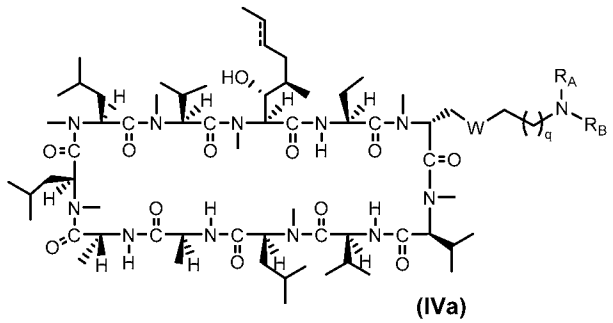
19. A compound of claim 1, having structure of Formulae (IIa)-(VIa):



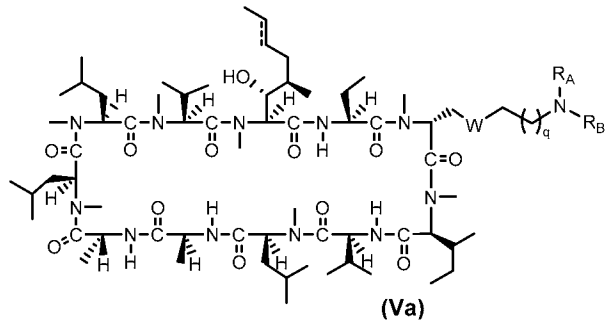
(IIa)



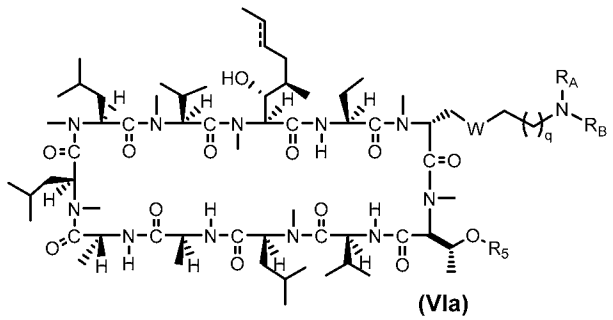
(IIIa)



(IVa)



(Va)



(VIa)

or a pharmaceutically acceptable salt thereof, wherein:

⁞ represents a single bond or double bond;

each W is independently O, S, or NR_1;

each R_1 is independently hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

each R_5 is independently:

H;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2$-$C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or (C_1-C_6)alkyl;

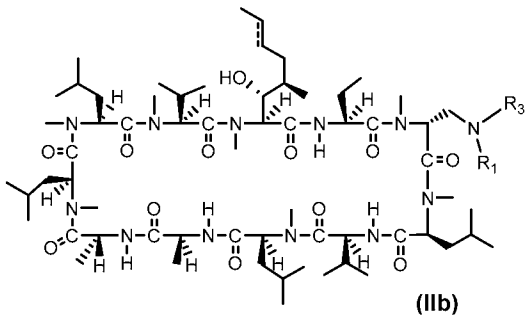
each occurrence of R_D is independently halogen, hydroxy, O(C_1-C_4)alkyl, C(=O)(C_1-C_4)alkyl, C(=O)O(C_1-C_4)alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5;

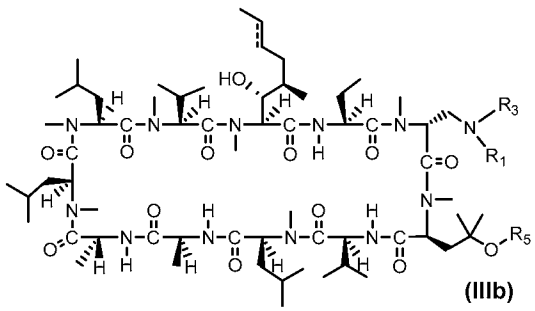
each of m and n is independently an integer of 1, 2, 3, 4 or 5; and

q is independently an integer of 7, 8, 9, 10, 11 or 12.

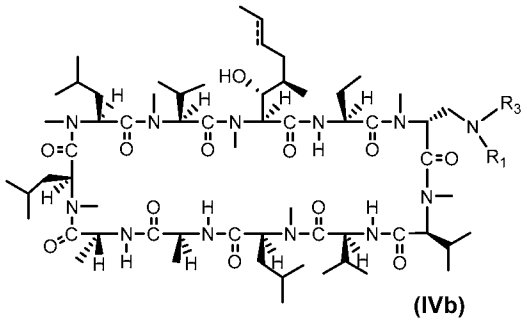
20. A compound of claim 1, having structure of Formulae (IIb)-(VIb):



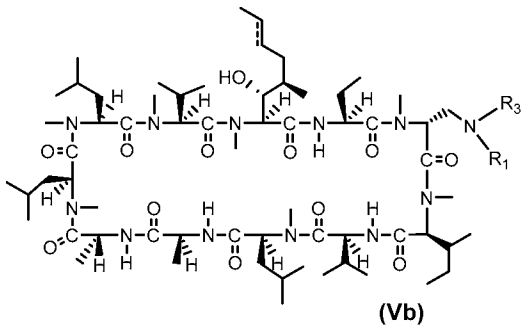
(IIb)



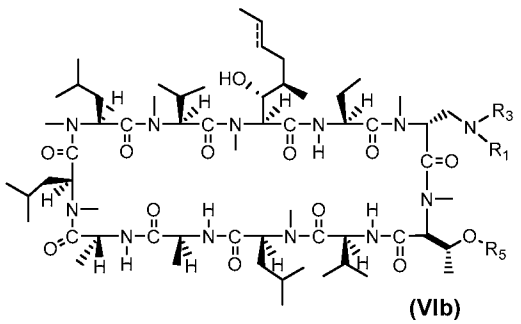
(IIIb)



(IVb)



(Vb)



(VIb)

or a pharmaceutically acceptable salt thereof, wherein:

represents a single bond or double bond;

each R_1 is independently hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1$-$C_6)$alkyl, $-C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_1 and R_3 together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of $(C_1$-$C_6)$alkyl, phenyl and benzyl;

each R_3 is independently:

$(C_7$-$C_{12})$alkyl, optionally substituted by one or more groups R_4 which may be the same or different, wherein one or more CH_2 moiety in the alkyl chain may be optionally substituted by O or S;

$(C_7$-$C_{12})$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $(CH_2)_mOH$, $(CH_2)_mO(CH_2)_mOH$, $(CH_2)_mNR_AR_B$, $(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_c(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$; or

$(C_7$-$C_{12})$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

each R_5 is independently:

H;

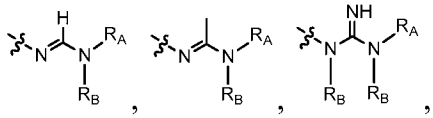
$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2$-$C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_4 is independently halogen, hydroxy, aryl, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)(C_1$-$C_6)$alkyl, $C(=O)OR_A$, $C(=O)NR_AR_B$, $-NR_AR_B$, $NR_CCH_2(CH_2)_pNR_AR_B$,  , $NR_C[CH_2(CH_2)_pNR_A]_mCH_2(CH_2)_nNR_AR_B$, $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nOR_A$, $OCH_2(CH_2)_pNR_AR_B$, or $O[CH_2(CH_2)_pO]_mCH_2(CH_2)_nNR_AR_B$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1\text{-}C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1\text{-}C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl;

$(C_3\text{-}C_7)$cycloalkyl optionally substituted with $(C_1\text{-}C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, $-O(C_1\text{-}C_6)$alkyl, $-C(=O)O(C_1\text{-}C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1\text{-}C_6)$alkyl;

each occurrence of R_D is independently halogen, hydroxy, $O(C_1\text{-}C_4)$alkyl, $C(=O)(C_1\text{-}C_4)$alkyl, $C(=O)O(C_1\text{-}C_4)$alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5; and

each of m, n and q is independently an integer of 1, 2, 3, 4 or 5.

21. The compound of claim 20, wherein R_1 is hydrogen or $(C_1$-$C_6)$alkyl, and R_3 is $(C_7$-$C_{12})$alkyl.

22. The compound of claim 5, wherein:

 represents a single bond or double bond;

each W is independently O, S, or NR_1;

each R_1 is independently hydrogen;

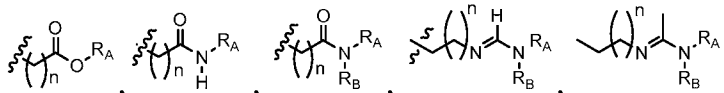
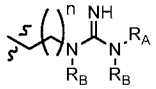
$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -O$(C_1$-$C_6)$alkyl, -C(=O)O$(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

each R_3 is independently  , or  ;

R_5 is:

H;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_6 which may be the same or different;

$(C_2$-$C_6)$alkenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, aryl, $(CH_2)_pOR_A$, $O(CH_2)_mOH$, $O(CH_2)_mO(CH_2)_mOH$, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $(CH_2)_pNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_AR_B$, $(CH_2)_pNR_C(CH_2)_mNR_c(CH_2)_mNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

$(C_2$-$C_6)$alkynyl, optionally substituted by one or one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

$(C_3$-$C_7)$cycloalkyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, amino, monoalkylamino and dialkylamino;

phenyl or CH_2-phenyl, optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$, $(CH_2)_pC(=O)OR_A$;

each occurrence of R_6 is independently halogen, hydroxy, aryl, $S(C_1$-$C_6)$alkyl, SR_A, OR_A, $O(CH_2)_mOR_A$, $O(CH_2)_mO(CH_2)_mOR_A$, $C(=O)OR_A$, $C(=O)NR_AR_B$, NR_AR_B, $O(CH_2)_mNR_AR_B$, $O(CH_2)_mO(CH_2)_mNR_AR_B$, $NR_C(CH_2)_mNR_AR_B$, or $NR_C(CH_2)_mNR_C(CH_2)_mNR_AR_B$, wherein said aryl or phenyl is optionally substituted by one or more groups which may be the same or different selected from halogen, hydroxy, $(C_1$-$C_6)$alkyl, $(CH_2)_pOR_A$, $(CH_2)_pNR_AR_B$, $(CH_2)_pC(=O)NR_AR_B$ and $(CH_2)_pC(=O)OR_A$;

each occurrence of R_A and R_B is independently:

hydrogen;

$(C_1$-$C_6)$alkyl, optionally substituted by one or more groups R_D which may be the same or different;

$(C_2$-$C_6)$alkenyl or $(C_2$-$C_6)$alkynyl;

$(C_3$-$C_7)$cycloalkyl optionally substituted with $(C_1$-$C_6)$alkyl;

phenyl optionally substituted with from one to five groups which may be the same or different selected from halogen, -$O(C_1$-$C_6)$alkyl, -$C(=O)O(C_1$-$C_6)$alkyl, amino, alkylamino and dialkylamino;

or a heterocyclic ring which may be saturated or unsaturated containing five or six ring atoms and from one to three heteroatoms which may be the same or different selected from nitrogen, sulfur and oxygen;

or R_A and R_B, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain another heteroatom selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to four groups which may be the same or different selected from the group consisting of alkyl, phenyl and benzyl;

each occurrence of R_C is independently hydrogen or $(C_1$-$C_6)$alkyl;

each occurrence of R_D is independently halogen, hydroxy, $O(C_1$-$C_4)$alkyl, $C(=O)(C_1$-$C_4)$alkyl, $C(=O)O(C_1$-$C_4)$alkyl;

each p is independently an integer of 0, 1, 2, 3, 4, or 5; and

each of m and q is independently an integer of 1, 2, 3, 4 or 5; and

n is independently an integer of 6, 7, 8, 9, 10, 11 or 12.

23. The compound of claim 19, wherein q is 1 or 2.

24. The compound of any one of claims 19-23, wherein W is O.

25. The compound of any one of claims 19-23, wherein W is S.

26. The compound of any one of claims 19-23, wherein W is NH.

27. The compound of any one of claims 19-23, wherein W is N-$(C_1$-$C_4)$alkyl.

28. The compound of any one of claims 19-27, wherein:

R_5 is H, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1$-$C_6)$alkyl, CH_2-O-$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)OR_A$, $(C_1$-$C_6)$-monoalkyl amine, $(C_1$-$C_6)$-dialkyl amine, or $(C_1$-$C_6)$-cyclic amine, in which said phenyl or benzyl is optionally substituted by one to three substitutents selected from $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, and halogen; and R_A is H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkylOH, $(CH_2)_pO(CH_2)_mOH$, $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkyl$O(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl; p is an integer of 0, 1, 2, 3, 4, or 5; and m is an integer of 1, 2, 3, 4 or 5.

29. The compound of any one of claims 19-27, wherein:

R_5 is H, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, phenyl, benzyl, CH_2-S-$(C_1$-$C_4)$alkyl, CH_2-O-$(C_1$-$C_4)$alkyl, $(CH_2)_2OH$, or $(CH_2)_2O(C_1$-$C_4)$alkyl.

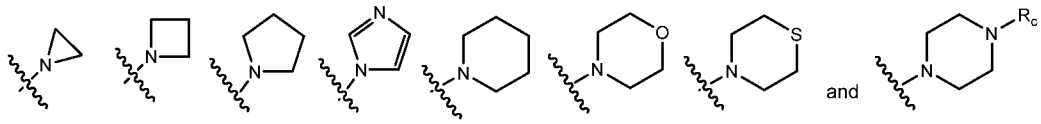
30. The compound of any one of claims 19-27, wherein R_5 is H.

31. The compound of any one of claims 19-27, wherein R_5 is methyl.

32. The compound of any one of claims 19-31, wherein each occurrence R_A and R_B is independently H, $(C_1$-$C_6)$alkyl, phenyl, CH_2-phenyl, $(C_1$-$C_6)$alkyl-OH, $(CH_2)_pO(CH_2)_mOH$, or $(CH_2)_pO(CH_2)_mO(CH_2)_mOH$, $(C_1$-$C_6)$alkyl-O-$(C_1$-$C_4)$alkyl, $(CH_2)_pO(CH_2)_mO(C_1$-$C_4)$alkyl, or $(CH_2)_pO(CH_2)_mO(CH_2)_mO(C_1$-$C_4)$alkyl.

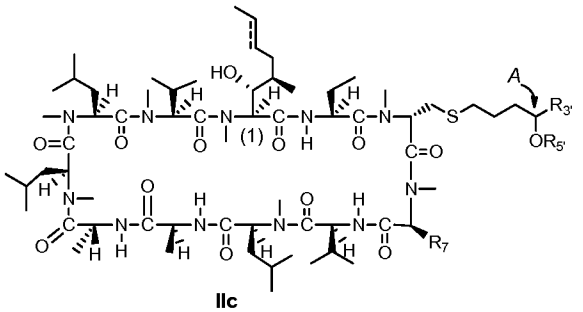
33. The compound of any one of claims 19-31, wherein each occurrence R_A and R_B is independently H or $(C_1$-$C_6)$alkyl.

34. The compound of any one of claims 19-31, wherein R_A and R_B, together with the nitrogen atom to which they are attached, form a heterocycle selected from

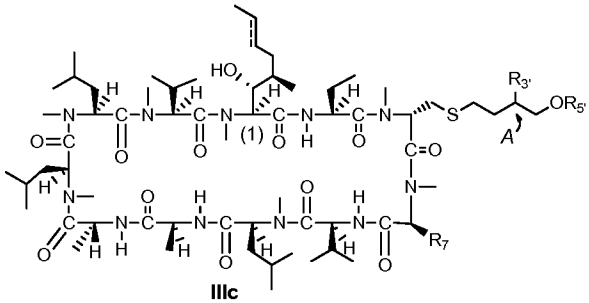


, in which R_C is H, Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, CH_2CMe_3, Ph, CH_2Ph, CH_2CH_2OH, or $CH_2CH_2O(C_1$-$C_4)$alkyl.

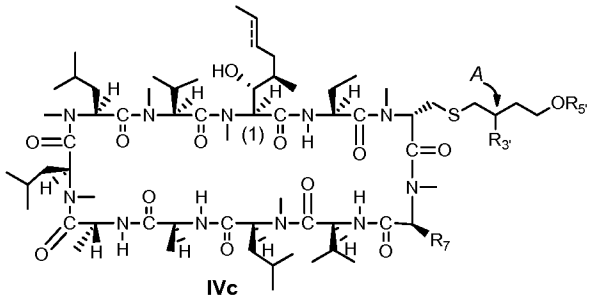
35. A compound of claim 1, having structure of Formulae (IIc)-(IVc):



IIc



IIIc

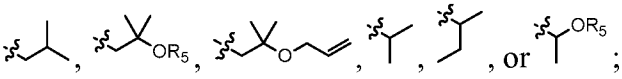


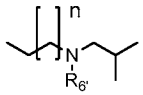
IVc

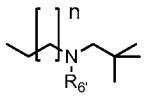
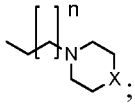
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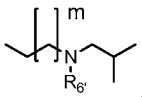
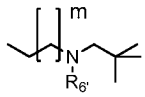
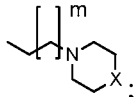
wherein

represents a single bond or double bond;

R_7 is  ;

$R_{3'}$ is Pr, i-Pr, $-CH_2(CH_2)_nNMe_2$, $-CH_2(CH_2)_nNEt_2$, $-CH_2(CH_2)_nOR_{5'}$,  ,

 , or  ;

R_5 and $R_{5'}$ are each independently H, Me, Et, Pr, *i*-Pr, $-CH_2(CH_2)_nNMe_2$, $-CH_2(CH_2)_nNEt_2$,  ,  , or  ;

$R_{6'}$ is H, Me, Et, Pr, i-Pr, i-Bu, or  ;

X is O, S, or $NR_{6'}$;

m is an integer of 1, 2, 3, 4, 5, or 6; and

n is an integer of 2, 3, 4, 5, or 6.

36. The compound of claim 35, wherein each of the chiral centers *A* in the compound independently has a R or S configuration.

37. A pharmaceutical composition comprising at least one compound according to any one of claims 1-36 and a pharmaceutically-acceptable carrier or diluent.

38. A method for treating or preventing a viral infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36.

39. A method for treating or preventing hepatitis C virus infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36.

40. A method for treating or preventing hepatitis B virus infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36.

41. A method for treating or preventing HIV infection in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36.

42. A method for inhibiting a cyclophilin in a subject in need thereof, the method comprising administrating to said subject an effective cyclophilin-inhibiting amount of at least one compound according to any one of claims 1-36.

43. A method for treating or preventing diseases that are mediated by cyclophilins in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36.

44. A method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36, wherein the diseases are selected from inflammation, respiratory inflammation, rheumatoid arthritis, and dry eye.

45. A method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36, wherein the diseases are selected from neurodegenerative diseases such as Alzheimer's disease, Parkinson's

disease, Huntington's Diseases, and ALS; traumatic brain injury; stroke; ischemia-reperfusion injury in the brain, heart, kidney, and myocardial infarction.

46. A method for treating or preventing diseases in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36, wherein the diseases are selected from cardiovascular diseases, vascular stenosis, atherosclerosis, abdominal aortic aneurysms, cardiac hypertrophy, aortic rupture, pulmonary arterial hypertension, myocarditis and myocardial fibrosis, and ischaemic heart diseases.

47. A method for treating or preventing diseases or conditions in a mammalian species in need thereof, the method comprising administering to the mammalian species a therapeutically effective amount of at least one compound according to any one of claims 1-36, wherein the diseases or conditions are selected from cancer, obesity, diabetes, muscular dystrophy, and hair loss.