(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
06 June 2019 (06.06.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/108591 A1

(51) International Patent Classification:

C07D 413/14 (2006.01)	*C07D 471/04* (2006.01)
A61K 38/15 (2006.01)	*C07D 487/04* (2006.01)
C07D 413/10 (2006.01)	*C07D 491/052* (2006.01)
C07K 11/02 (2006.01)	*C07D 498/04* (2006.01)
A61P 33/00 (2006.01)	*C07D 513/04* (2006.01)
C07D 417/14 (2006.01)	*A01N 43/72* (2006.01)

(21) International Application Number:
PCT/US2018/062749

(22) International Filing Date:
28 November 2018 (28.11.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/591,942 29 November 2017 (29.11.2017) US

(71) Applicant: **ZOETIS SERVICES LLC** [US/US]; 10 Sylvan Way, Parsippany, NJ 07054 (US).

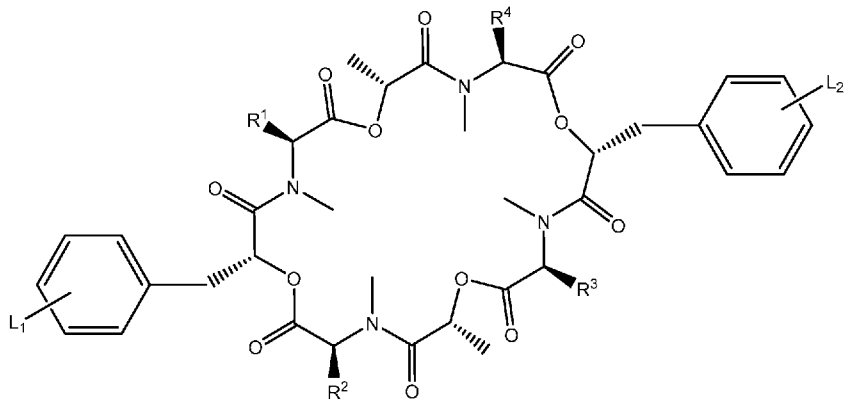
(72) Inventors: **CURTIS, Michael P.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **SHEEHAN, Susan M.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **KYNE, Graham M.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **BEDORE, Matthew W.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **EWIN, Richard A.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **JOHNSON, Paul D.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **MCTIER, Tom L.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **KNAUER, Christopher S.**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US). **VAIRAGOUNDAR, Rajendran**; c/o Zoetis Services LLC, 333 Portage Street, Kalamazoo, MI 49007 (US).

(74) Agent: **MISIAK, Paul M.** et al.; c/o Zoetis Services LLC, 10 Sylvan Way, Parsippany, New Jersey 07054 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: ENDOPARASITIC DEPSIPEPTIDES



(1)

(57) Abstract: The present invention provides cyclic depsipeptides of Formula (1), stereoisomers thereof, and veterinary acceptable salts thereof (1) wherein each of R^1, R^2, R^3, R^4, L_1, and L_2, are as defined herein. The present invention also contemplates compositions and methods of treatment as an endoparasiticide with a Formula (1) compound.

WO 2019/108591 A1

[Continued on next page]

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

ENDOPARASITIC DEPSIPEPTIDES

Field of the Invention

The present invention is directed to new endoparasitic depsipeptide compounds with improved activity against endoparasites. The invention is also directed to compositions comprising the compounds, methods and uses of the compounds for eradicating, controlling, treating and preventing a parasite infestation and/or infection in animals. The compounds of the invention may be administered to animals, particularly non-human animals, to prevent or treat parasitic infections.

Background

Animals, such as non-human mammals, for example, companion animals and livestock, are often susceptible to parasite infestations. These parasites may be endoparasites including for example, helminthiasis which is most frequently caused by a group of parasitic worms described as nematodes or roundworms. These parasites cause severe economic losses in pigs, sheep, horses, and cattle as well as affecting companion animals (*e.g.* cats and dogs). Other parasites include those which occur in the gastrointestinal tract of animals and humans include Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Toxocara, Toxascaris, Trichuris, Enterobius and parasites which are found in the blood or other tissues and organs such as filarial worms and the extra intestinal stages of Strongyloides, Toxocara and Trichinella.

One type of endoparasite which seriously harms animals is *Dirofilaria immitis,* also known as heartworm. Other filarial endoparasites include *Dirofilaria repens* and *Dirofilaria honkongensis,* which can also infect humans. The most common hosts are dogs and cats but other mammals such as ferrets and raccoons may also be infected. Heartworms go through several life stages before they become adults infecting the pulmonary artery of the host mammal. The worms require the mosquito as an intermediate host to complete their life cycle. The period between the initial infection when the dog is bitten by a mosquito and the maturation of the worms into adults living in the heart and pulmonary arteries is six to seven months in dogs and is known as the "prepatent period". L3 larvae migrate during blood feeding of the mosquito to the tip of the mosquito's mouth

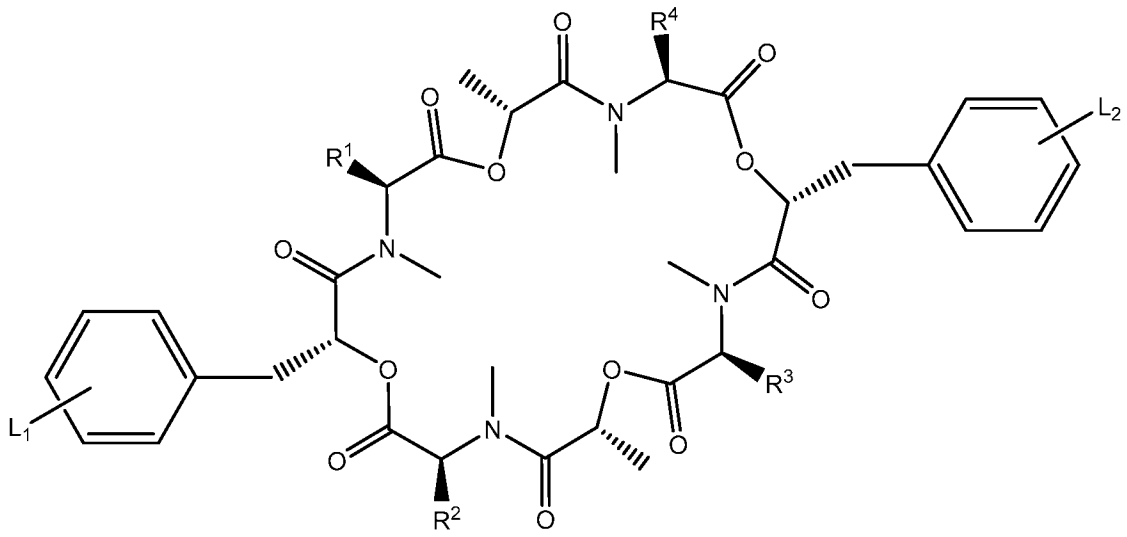
parts (labium), leave the mosquito and are deposited on the skin of the dog where they then migrate through the bite wound into the host. Most L3 larvae molt to fourth-stage larvae (L4s) in canine subcutaneous tissues within 1-3 days after infection. Then, they migrate to the muscles of the chest and abdomen, and 45 to 60 days after infection, molt to the fifth stage (LS, immature adult). Between 75 and 120 days after infection, these immature heartworms then enter the bloodstream and are carried through the heart to reside in the pulmonary artery. Around seven months after infection, *Dirofilaria immitis* adults reach maturity and sexually reproduce in the pulmonary arteries and right ventricle. Adult males are around 15cm in length, and females are around 25cm in length and their normal life span as adults is calculated to be about 5 years.
Heartworm infection is a severe and life-threatening disease. Canine heartworm infection is preventable and prophylaxis treatment is a priority in heartworm endemic areas. Treatment of mature heartworm infection with an adulticide *(e.g.* melarsomine dihydrochloride) is costly and can cause serious adverse side effects, thus prevention by monthly administration of drugs that interrupt larvae development is widely used. The goal of marketed heartworm preventive therapies in dogs is to prevent the development of the parasite to adult heartworms by interrupting the *Dirofilaria immitis* life cycle post-infection.
The macrocyclic lactones (MLs, *e.g.* ivermectin, eprinomectin, milbemycin ox1me, moxidectin, and selamectin) are the most commonly used chemoprophylaxis agents and are administered at monthly or six-month intervals. These drugs have been effective against *Dirofilaria immitis* infective third-stage larvae (L3) deposited by the mosquito as well as maturing fourth-stage larvae (L4). When administered monthly, MLs kill L3 and L4 larvae acquired within the previous 30 days, and thus prevent disease caused by adult worms. MLs can also be used monthly in infected dogs to suppress reproduction in adult worms and remove microfilariae, thereby reducing transmission and gradually causing the attrition of adult worms (Vet. Parasitol.2005, 133(2-3), 197-206).

In recent years, an increased number of lack of efficacy cases have been reported, in which dogs develop mature heartworm infections despite receiving monthly prophylactic doses of macrocyclic lactone drugs. For example, Atkins *et al.*, (Vet. Parasitol. 206 (2014) 106-113) recently reported that an increasing number of cases of dogs that tested heartworm antigen positive while

receiving heartworm preventive medication which suggests that some populations of *Dirofilaria immitis* have developed selectional resistance to heartworm preventives (American Heartworm Society, 2010. Heartworm Preventive Resistance. Is it Possible, vol. 37. Bulletin of the American Heartworm Society, pp. 5.). Thus, there is an ongoing need to develop new anthelmintic agents with improved activity against *Dirofilaria immitis* and other endoparasites.
Various parasiticides exist in the art for treating endoparasites infections in animals. In addition to the macrocyclic lactones, cyclic depsipeptides with antiparasitic activity are known . PF1022A, a 24-membered cyclooctadepsipeptide isolated from the fungus *Mycelia sterilia* by Sasaki *et al (see J Antibiotics* 45: 692-697 (1992)), has been found to exhibit broad anthelmintic activity against a variety of endoparasites *in vivo* with low toxicity These compounds are described, for example, in U.S. Patent Nos. 5,514,773; 5,747,448; 5,646,244; 5,874,530; among others, which are incorporated herein by reference.
Emodepside is a semi synthetic analog of PF1022A containing a morpholine group at the *para* position of the aryl ring in the phenyl lactate groups. Emodepside is a potent anthelmintic used in combination with praziquantel in the product Profender® for the treatment of parasitic worms in cats and dogs. However, the antiparasitic activity of PF 1022A and emodepside is not satisfactory for the treatment of certain parasites, especially for the control of *Dirofilaria immitis* in mammals to prevent the establishment of heartworm disease. Thus, there is a need in the art for more effective antiparasitic agents for treatment and protection of animals, *e.g.* mammals, fish and birds against parasites, in particular internal parasites including nematodes and filarial worms such as heartworm.

Summary of the Invention

The invention provides novel and inventive cyclic depsipeptide compounds with selective anthelmintic activity against L3 and L4 staged endoparasites. In addition, the invention provides compositions comprising the depsipeptide compounds and methods and uses for the treatment and prevention of parasitic infection and possibly infestation of animals using the compounds.
In one aspect, the present invention provides cyclic depsipeptide Formula (1) compounds, shown below:



(1)

wherein

L_1 and L_2 are each individually and separately C_1-C_4alkylheteroaryl and C_1-C_4alkylheterocycle, wherein the heteroaryl moiety is a 5- or 6-member monocyclic aromatic ring or a 8- to 11-member fused aromatic ring each containing at least one heteroatom selected from N, O, and S; and the heterocycle moiety is a 4- to 6-member monocyclic saturated or partially saturated ring or a 8- to 11-member fused saturated or partially saturated ring, and wherein the heteroaryl and heterocycle moiety are N-linked to the alkyl;

and wherein the L_1 and L_2 alkyl moiety of the alkylheteroaryl and alkylheterocycle is optionally substituted with at least one substituent selected from the group consisting of halo, C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_4alkoxy, C_3-C_6cycloalkyl, and nitro; or at least two alkyl substitutions of each of the L_1 and L_2 alkyl moieties can join together to each form a C_3-C_6cycloalkyl ring;

or L_1 is absent;

and wherein the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, wherein the alkyl, alkenyl and alkynyl groups are independently and separately optionally substituted with at least one substituent selected from hydroxyl, cyano, C_3-C_6 cycloalkyl, -NR^aR^b, C_1-C_4alkoxy, morpholine, and phenyl;

or halo, cyano, nitro, $-NR^aR^b$, oxo, hydroxyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, saturated or partially saturated C_3-C_6cycloalkyl optionally substituted with at least one substituent selected from C_1-C_3alkyl, amino, cyano, halo, and C_1-C_3alkoxy;

or phenyl optionally substituted with at least one substituent selected from halo, cyano, C_1-C_4alkyl, and C_1-C_4alkoxy;

or a saturated or partially saturated 4- to 6-membered heterocycle ring containing at least one heteroatom selected from N, O, and S and further optionally substituted with C_1-C_4alkyl;

or a 5- to 6-membered heteroaryl ring containing at least one heteroatom selected from N, O, and S and further optionally substituted with at least one substituent selected from halo, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl and C_1-C_4alkoxy;

or -C(O)R, -COR, -C(O)OR, $-CS(O)_pR^a$, $-C(O)NR^aR^b$, -SR, -C(O)X, -OX, $-S(O)_pR$, $-S(O)_pX$, $-CNR^aC(O)R$, $CNR^aC(O)OR$, $-CNR^aR^b$, $-CNH_2(N)OH$, $-NR^aC(O)R$, $-NR^aC(O)OR$, $-NR^aS(O)_pR$, $-NR^aC(O)NR^aR^b$, $-OR^e$ $-OR^eNR^aC(O)OR^e$, $-OR^eC(O)OH$;

R is C_1-C_6alkyl, amino, C_1-C_6haloalkyl, phenyl optionally substituted with at least one substituent selected from C_1-C_3alkoxy, cyano, halo, C_1-C_3alkyl, and C_1-C_3haloalkyl;

R^1, R^2, R^3, and R^4 are each separately and independently H and C_1-C_6alkyl;

R^a and R^b are each separately H, C_1-C_6alkyl, C_1-C_3haloalkyl, C_3-C_6cycloalkyl, and phenyl optionally substituted with halo, amino, and C_1-C_3haloalkyl;

R^e is C_1-C_6alkyl optionally substituted with halo, amino, C_3-C_6cycloalky,and C_1-C_4alkoxy;

X is an N-linked 4- to 6-membered saturated or partially saturated heterocyclic ring optionally containing at least one additional heteroatom selected from N, O, and S; or X is a 5- to 6-membered heteroaryl ring containing at least one heteroatom selected from N, O, and S; or X is phenyl optionally substituted with at least one substituent selected from C_1-C_4haloalkyl, halo, amino, cyano, C_1-C_4alkyl, and C_1-C_4alkoxy; or X is a saturated or partially saturated C_3-C_6 cycloalkyl ring; and

p is the integer 0, 1, or 2, stereoisomers thereof, and veterinary acceptable salts thereof.

In one aspect of the invention, L_1 and L_2 are each separately C_1alkylheteroaryl (C_1heteroaryl) and C_1alkylheterocycle (C_1heterocycle). In another aspect of the invention, L_1 and L_2 are C_1heteroaryl. In one aspect of the invention, L_1 and L_2 are each C_1heteroaryl and are both attached to the para-carbon of the phenyl ring. In one aspect of the invention, L_1 and L_2 are each C_1heteroaryl and L_1 is attached to the meta-carbon of the phenyl ring and L_2 is attached to the para-carbon of the phenyl ring. In one aspect of the invention, L_1 and L_2 are each C_1heteroaryl and L_1 is attached to the ortho-carbon of the phenyl ring and L_2 is attached to the para-carbon of the phenyl ring. In one aspect of the invention, L_1 and L_2 are each C_1heteroaryl and L_1 and L_2 are both attached to the meta-carbon of the phenyl ring. In yet another aspect of the invention, L_1 is absent and L_2 is C_1heteroaryl. In yet another aspect of the invention, L_1 is absent and L_2 is C_1heteroaryl attached to the para-carbon of the phenyl ring. In yet another aspect of the invention, L_1 is absent and L_2 is C_1heteroaryl attached to the meta-carbon of the phenyl ring. Preferrably, in one aspect, L_1 and L_2 are both heteroaryl and are attached to the para-carbon of the phenyl ring.

In another aspect of the invention, L_1 and L_2 are C_1heterocycle. In one aspect of the invention, L_1 and L_2 are each C_1heterocycle and L_1 and L_2 are both attached to the para-carbon of the phenyl ring. In one aspect of the invention, L_1 and L_2 are each C_1heterocycle and L_1 is attached to the meta-carbon of the phenyl ring and L_2 is attached to the para-carbon of the phenyl ring. In one aspect of the invention, L_1 and L_2 are each C_1heterocycle and L_1 is attached to the ortho-carbon of the phenyl ring and L_2 is attached to the para-carbon of the phenyl ring. In one aspect of the invention, L_1 and L_2 are each C_1heterocycle and L_1 and L_2 are both attached to the meta-carbon of the phenyl ring. In yet another aspect of the invention, L_1 is absent and L_2 is C_1heterocycle. In yet another aspect of the invention, L_1 is absent and L_2 is C_1heterocycle attached to the para-carbon of the phenyl ring. In yet another aspect of the invention, L_1 is absent and L_2 is C_1heterocycle attached to the meta-carbon of the phenyl ring. Preferrably, in one aspect, L_1 and L_2 are both heterocycle and are attached to the para-carbon of the phenyl ring.

In another aspect of the invention, L_1 is C_1heteroaryl and L_2 is C_1heterocycle. In each case, L_1 and L_2 are separately and individually attached to the respective para-carbon, meta-carbon, or ortho-carbon on the phenyl ring with the N atom of the hetero ring.

In one aspect of the invention, the L_1 and L_2 heteroaryls are each independently selected from a 5- to 6-member monocyclic ring or a 8- to 11-member fused ring each containing at least one heteroatom selected from N, O, and S. In another aspect of the invention the L_1 and L_2 heteroaryls include pyrrole, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, oxadiazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, indole, benzimidazole, indazole, benzotriazole, pyrrolo[2,3-b]pyridine, pyrrolo[2,3-c]pyridine, 3,4-dihydro-2H-benzo[b][1,4]oxazine, 1H-benzo[d]triazole, pyridine-2(1H)-one, 2,3-dihydroquinoline, 3,4-dihydro-2H-benzo[b][1,4]oxazine, 1H-pyrrolo[2,3-b]pyridine, 1H-pyrrolo[2,3-c]pyridine, 3H-[1,2,3]triazolo[4,5-c]pyridine, pyridine, pyrimidine, and the like. In yet another aspect of the invention, the L_1 and L_2 heteroaryls include pyrrole, pyrazole, imidazole, thiazole, triazole, tetrazole, pyridine, and pyrimidine. In yet another aspect of the invention, the L_1 and L_2 heteroaryls include pyrazole, imidazole, and thiazole. In yet another aspect of the invention, the L_1 and L_2 heteroaryls are pyrazole and imidazole. In yet another aspect of the invention, the L_1 and L_2 heteroaryls are pyrazole. In yet another aspect of the invention, the L_1 and L_2 heteroaryls are imidazole. The L_1 and L_2 heteroaryls are optionally substituted as described herein.

In another aspect of the invention, the L_1 and L_2 heterocycles are each independently selected from a 4-, 5-, or 6-member monocyclic saturated or partially saturated ring or a 8- to 11-member fused saturated or partially saturated ring, each containing at least one heteroatom selected from N, O, and S. In yet another aspect of the invention, the L_1 and L_2 heterocycles include azetidine, pyrrolidine, piperidine, morpholine, piperazine, azathiane, imidazolidine, oxazolidine, tetrahydropyran, 1,2,3,4-tetrahydropyridine, 1,2,5,6-tetrahydropyridine, thiomorpholine, 2,4,5,6-tetrahydrocyclopenta[c]pyrrole, 1,2,3,5-tetrahydropyrrolo[3,4-c]pyrrole, 2,3,3a,4,5,6,-hexahydrocyclo-pental[c]pyrazole, 1,3a,4,5,7,7a-hexahydropyrano[3,4-c]pyrazole, 1,3-oxazinane, and the like. In yet another aspect of the invention, the L_1 and L_2 heterocycles include pyrrolidine, piperidine, morpholine, piperazine, azathiane, and oxazolidine. In yet another aspect of the invention, the L_1 and L_2 heterocycles include pyrrolidine, piperidine, morpholine, and piperazine. In yet another aspect of the invention, the L_1 and L_2 heterocycles include pyrrolidine, piperidine, and morpholine. In yet another aspect of the invention, the L_1 and L_2 heterocycles are pyrrolidine. In yet another aspect of the invention, the L_1 and L_2 heterocycles are

piperidine. In yet another aspect of the invention, the L_1 and L_2 heterocycles are morpholine. The L_1 and L_2 heterocycles are optionally substituted as described herein.

In yet another aspect of the invention, R^1, R^2, R^3, and R^4 are each separately and independently H, methyl, ethyl, propyl, isopropyl, butyl, and isobutyl. In yet another aspect of the invention, R^1, R^2, R^3, and R^4 are each separately and independently methyl, ethyl, propyl, and isopropyl. In yet another aspect of the invention, R^1, R^2, R^3, and R^4 are each separately and independently methyl, ethyl, and isopropyl. In yet another aspect of the invention, R^1, R^2, R^3, and R^4 are isopropyl.

In yet another aspect of the invention, the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, wherein the alkyl, alkenyl and alkynyl groups are independently and separately optionally substituted with hydroxyl, bromo, fluoro, chloro, iodo, amino, cyano, cyclopropyl, and phenyl; halo, cyano, nitro, amino, hydroxyl, $-CHF_2$, $-CF_3$, $-CH_2F$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CF_3$; cyclopropyl, cyclobutyl, and cyclopentyl, each optionally substituted with at least one methyl, ethyl, halo, methoxy, ethoxy, amino, and cyano; cyclopentene, cyclohexene, oxetane, tetrahydro-2H-pyran, morpholine; furan, thiazole, triazolyl, thiophenyl, pyrrole, pyridine, pyrimidine, and pyrazine each optionally substituted with at least one substituent selected from methyl, methoxy, and ethoxy; phenyl optionally substituted with halo, methoxy, and methyl; methoxy, ethoxy, isopropoxy, isobutoxy, oxo, $-C(O)N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)C(CH_3)_3$, $-C(O)CH(CH_3)_2$, $-C(O)OCH_2CH_3$, $-C(O)OC(CH_3)_3$, $-C(O)OC(CH_3)_2$, -C(O)N-cyclopropyl, $-CH_2NHC(O)OC(CH_3)_3$, $-CH_2NHC(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-NHC(O)OCH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, $-NHC(O)OC(CH_3)_3$, $-NHC(O)OCH_2CF_3$, $-NHC(O)NH-C(CH_3)_3$, and -NHC(O)NH-phenyl optionally substituted with $-CF_3$; -C(O)-azetidine, -C(O)-pyrrolidine, -C(O)-piperidine, -C(O)-morpholine, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-SC(CH_3)_2$, $-S(O)_2$-azetidine, $-S(O)_2$-pyrrolidine, $-S(O)_2$-piperidine, $-S(O)_2$-morpholine, $-OCHF_2$, $-OCH_2F$, $-OCF_3$, $-OCH_2CF_3$, $-OCH_2$-cyclopropyl, -O-cyclopropyl, -O-cyclobutyl, -O-cyclopentyl, -O-oxetane, $-OCH_2OCH_3$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2C(O)OH$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NC(O)OC(CH_3)_3$; O-thiazole, O-pyridine, each optionally substituted with methyl, halo, and methoxy.

In yet another aspect of the invention, the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from C_1-C_6alkyl optionally substituted with hydroxyl, bromo, fluoro, chloro, iodo, amino, cyano, cyclopropyl, and phenyl; halo, cyano, nitro, amino, hydroxyl, $-CHF_2$, $-CF_3$, $-CH_2F$; cyclopropyl, cyclobutyl, and cyclopentyl, each optionally substituted with at least one methyl, ethyl, halo, methoxy, ethoxy, amino, and cyano; oxetane, morpholine; phenyl optionally substituted with halo, methoxy, and methyl; methoxy, ethoxy, isopropoxy, isobutoxy, oxo, $-C(O)N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)C(CH_3)_3$, $-C(O)CH(CH_3)_2$, $-C(O)OCH_2CH_3$, $-C(O)OC(CH_3)_3$, $-C(O)OC(CH_3)_2$, $-CH_2NHC(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-NHC(O)OCH_3$, $-NHC(O)CH_3$, $-NHS(O)_2CH_3$, $-NHC(O)OC(CH_3)_3$, $-NHC(O)NH-C(CH_3)_3$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, $-SC(CH_3)_2$, $-OCHF_2$, $-OCH_2F$, $-OCF_3$, $-OCH_2CF_3$, $-OCH_2OCH_3$, $OCH_2CH_2OCH_3$, $-OCH_2$-cyclopropyl, -O-cyclopropyl, -O-cyclobutyl, -O-cyclopentyl, and -O-oxetane.

In yet another aspect of the invention, the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from C_1-C_6alkyl optionally substituted with hydroxyl, bromo, fluoro, chloro, iodo, and cyclopropyl; halo, methoxy, ethoxy, isopropoxy, isobutoxy, hydroxyl, $-CHF_2$, $-CF_3$, $-CH_2F$; cyclopropyl, cyclobutyl, and cyclopentyl, each optionally substituted with at least one methyl, halo, methoxy, and ethoxy; oxetane; morpholine; $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)C(CH_3)_3$, $-C(O)CH(CH_3)_2$, $-CH_2NHC(O)CH_3$, $-S(O)_2CH_3$, $-SC(CH_3)_2$, $-OCHF_2$, $-OCH_2F$, $-OCF_3$, $-OCH_2CF_3$, $-OCH_2OCH_3$, $OCH_2CH_2OCH_3$, $-OCH_2$-cyclopropyl, -O-cyclopropyl, -O-cyclobutyl, -O-cyclopentyl, and -O-oxetane.

In yet another aspect of the invention, the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from methyl, ethyl, propyl, isopropyl, t-butyl, sec-butyl, amino, $-CH_2F$, $-CHF_2$, $-CF_3$; $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CN$, cyclopropyl, methoxy, ethoxy, isopropoxy, hydroxyl, cyano, amino, and halo; and wherein the cyclopropyl moiety is optionally substituted with at least one sbstituent selected from methyl, fluoro, chloro, bromo, methoxy, and ethoxy.

In yet another aspect of the invention, the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from C_1-C_6alkyl, halo, cyano, C_1-C_6haloalkyl, C_3-

C_6cycloalkyl optionally substituted with at least one substituent selected from fluoro, chloro, methyl, and methoxy; C_1-C_6alkoxy, phenyl optionanlly substituted with at least one substituent selected from halo and methoxy; -C_1-cyclopropyl, and C_2-C_6alkynl optionally substituted with cyclopropyl or phenyl. In yet another aspect of the invention, the L_1 and L_2 heteroaryl, and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from methyl, ethyl, propyl, isopropyl, t-butyl, isobutyl, sec-butyl, cyano, bromo, fluoro, chloro, iodo, -CH_2F, -CHF_2, -CF_3; cyclopropyl, cylobutyl, cyclopentyl, each optionally substituted with at least substituent selected from fluoro, chloro, methyl, and methoxy; methoxy, ethoxy, isopropoxy, isobutoxy; phenyl optionanlly substituted with at least one substituent selected from halo and methoxy; C_2-C_6alkynl optionally substituted with cyclopropyl or phenyl; pyrrole optionally substituted with at least one substituent selected from cyano and methyl.

In yet another aspect of the invention, the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with a 10-membered fused partially saturated heterocyclic ring containing at least one heteroatom selected from the N, O, and S, and wherein said ring is optionally substituted with oxo.

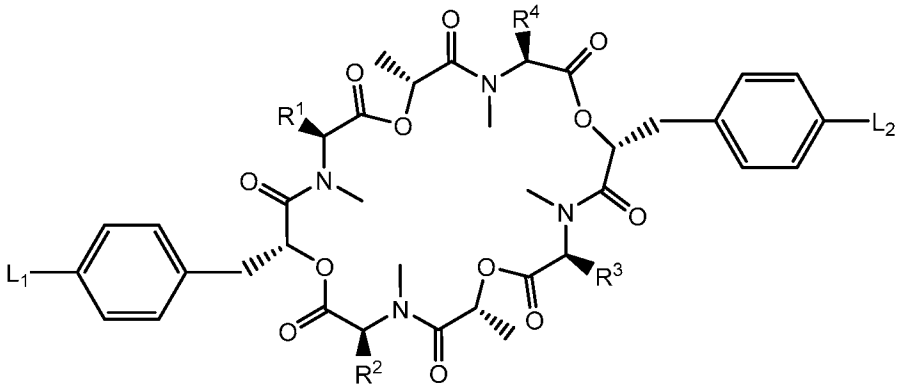
In yet another aspect of the invention, R^a and R^b are each separately H, methyl, ethyl, propyl, isopropyl, isobutyl, -CH_2F, -CHF_2, -CF_3, -CH_2CHF_2, -CH_2CF_3, cyclopropyl, cyclobutyl; and phenyl optionally substituted with fluoro, chloro, amino, and -CF_3.

In yet another aspect of the invention, R^e is methyl, ethyl, propyl, isopropyl, butyl and isobutyl, each optionally substituted with fluoro, chloro, amino, cyclopropyl, cyclobutyl, methoxy, ethoxy, and isopropoxy.

In yet another aspect of the invention, X is an N-linked 4- to 6-membered heterocyclic ring selected from azetidine, pyrrolidine, piperidine, and morpholine. In yet another aspect of the invention, X is a 5- to 6-membered heteroaryl ring selected from thiazolyl and pyridinyl. In yet another aspect of the invention, X is phenyl optionally substituted with at least one substituent selected from -CF_3, fluoro, chloro, amino, cyano, methyl, ethyl, methoxy, and ethoxy. In yet another aspect of the invention, X is a saturated or partially saturated C_3-C_6 cycloalkyl ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentane, and cyclohexene.

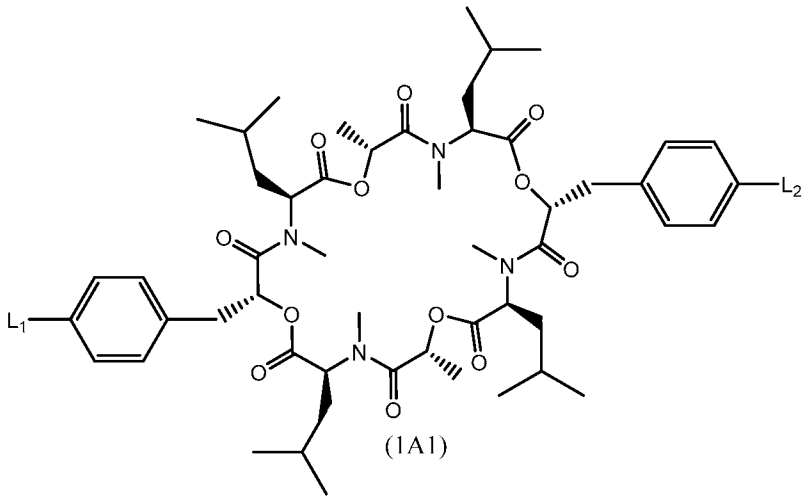
In yet another aspect of the invention, p is the integer 0. In yet another aspect, p is the integer 1. In yet another aspec of the invention, p is the integer 2.

In yet another aspect of the invention, is a compound of Formula (1) that is a Formula (1A) compound



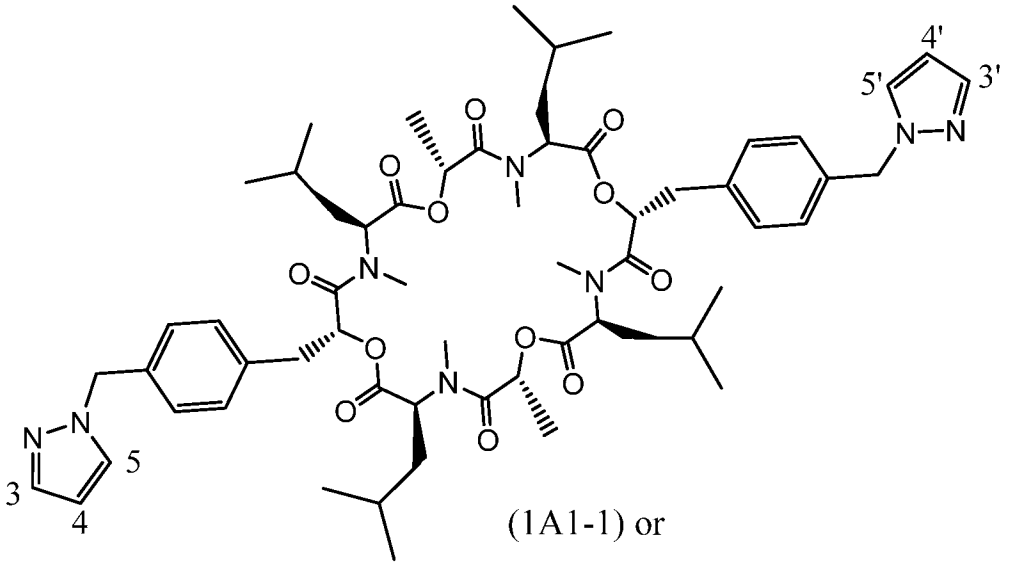
(1A)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1A) compound that is a Formula (1A1) compound

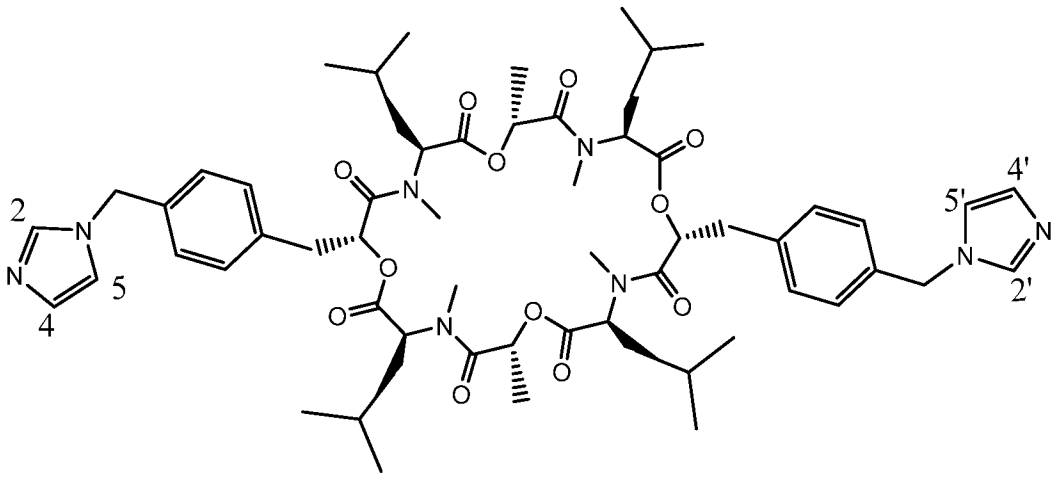


(1A1)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1A1) that is a Formula (1A1-1) or Formula (1A1-2) compound,



(1A1-1) or



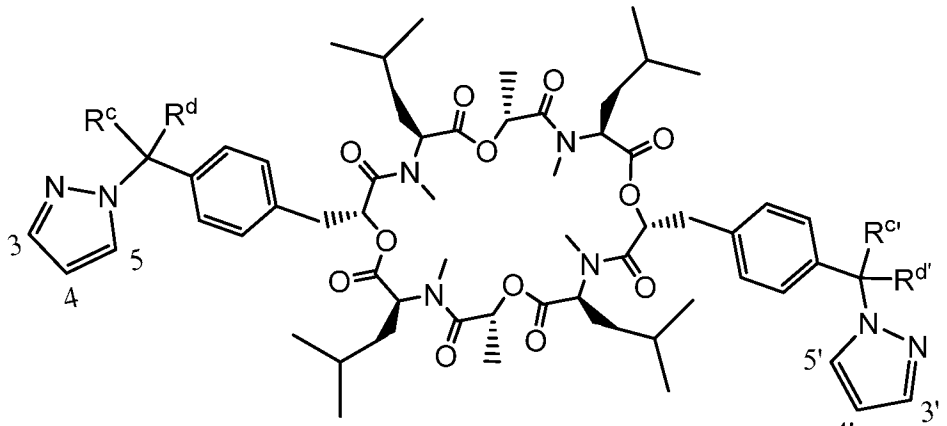
(1A1-2)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1A1-1) compound, stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1A1-1) selected from those compounds presented in Table 1a and Table 1b. In yet another aspect of the invention, are compounds of Formula (1A1-1) selected from those compounds presented in Table 1a. In yet another aspect of the invention, are compounds of Formula (1A1-1) selected from those compounds presented in Table 1b. In yet another aspect of the invention are Formula (1A1-1) compounds (example #) selected from the group consisting of: ((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis({4-[(3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl]phenyl}methyl)-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-

methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone) (1b-14); ((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-ethoxypyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone) (1b-21); ((3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-(pyrazol-1-ylmethyl)phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone) (1b-23); ((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone) (1b-108); ((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone) (1b-211); ((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(1-fluorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone) (1b-215); ((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(2,2-difluorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone) (1b-216); and ((3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(2-methylcyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone) (1b-222); stereoisomers thereof, and veterinary acceptable salts thereof.

In yet another aspect of the invention, is a Formula (1A1-2) compound, stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1A1-2) selected from those compounds presented in Table 6. In yet another aspect of the invention, are compounds of Formula (1A1-1) presented in Table 1 (1a and 1b) and Formula (1A1-2) compounds presented in Table 6.

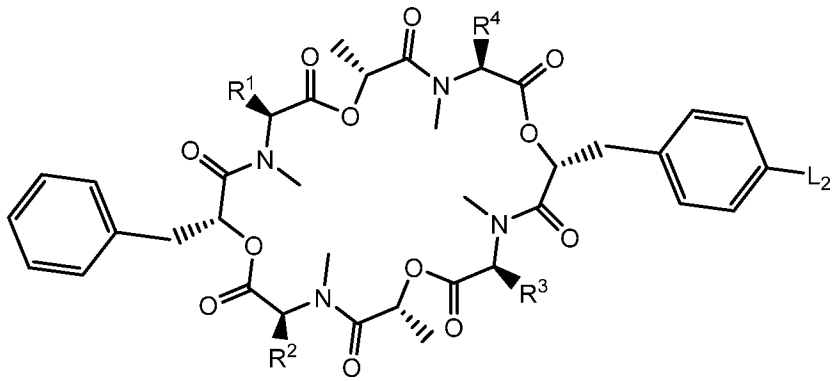
In yet another aspect of the invention, is a Formula (1) compound that is a Formula (1A1-3) compound, stereoisomers thereof, and veterinary acceptable salts thereof.



(1A1-3)

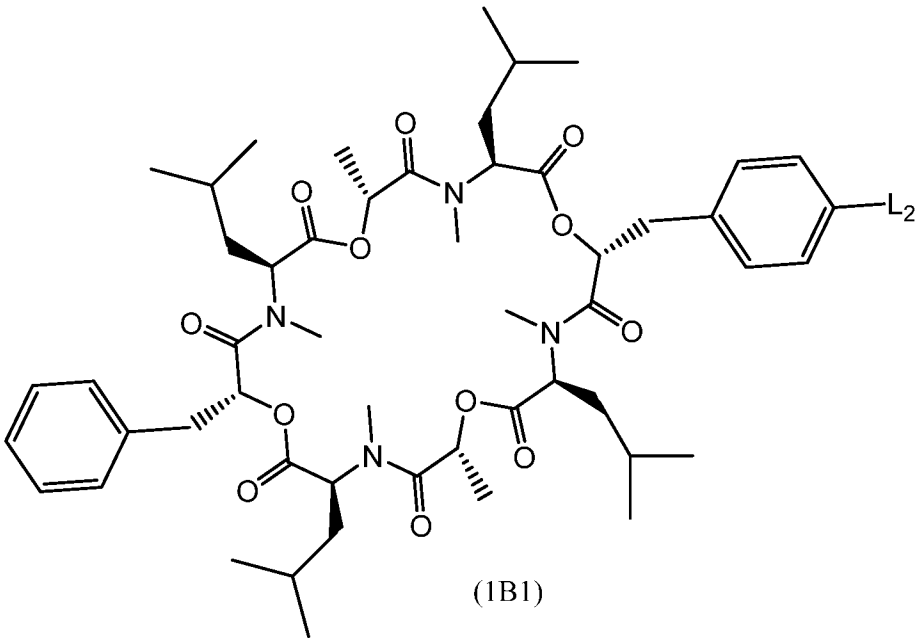
In yet another aspect of the invention, are compounds of Formula (1A1-3) selected from those compounds presented in Table 1c. In yet another aspect of the invention is the Formula (1A1-3) compound (example #), ((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(1-(1H-pyrazol-1-yl)cyclobutyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone) (1c-1), stereoisomers thereof, and veterinary acceptable salts thereof.

In yet another aspect of the invention, is a Formula (1) compound that is a Formula (1B) compound



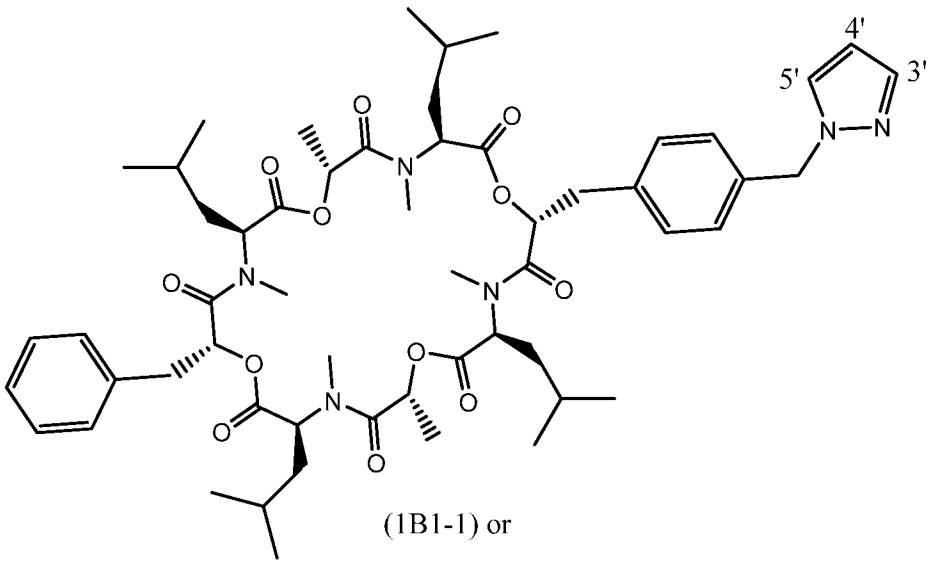
(1B)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1B) compound that is a Formula (1B1) compound

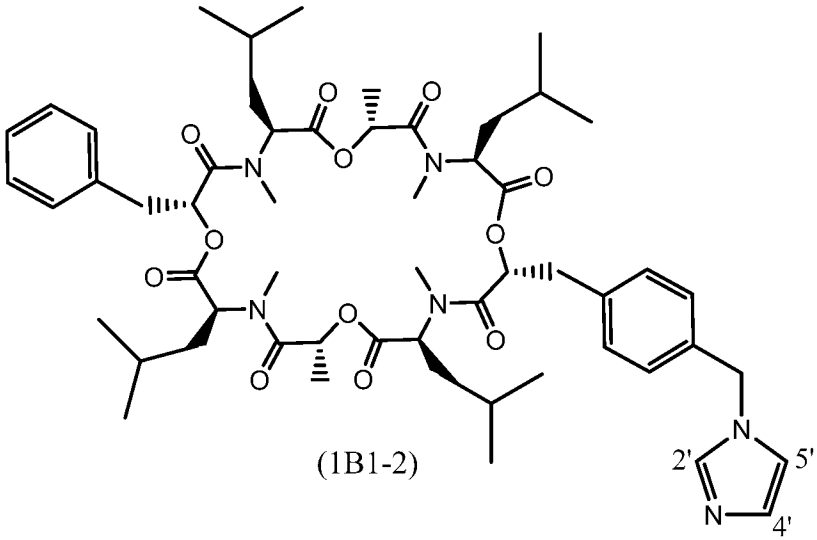


(1B1)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1B1) compound that is a Formula (1B1-1) or Formula (1B1-2) compound,



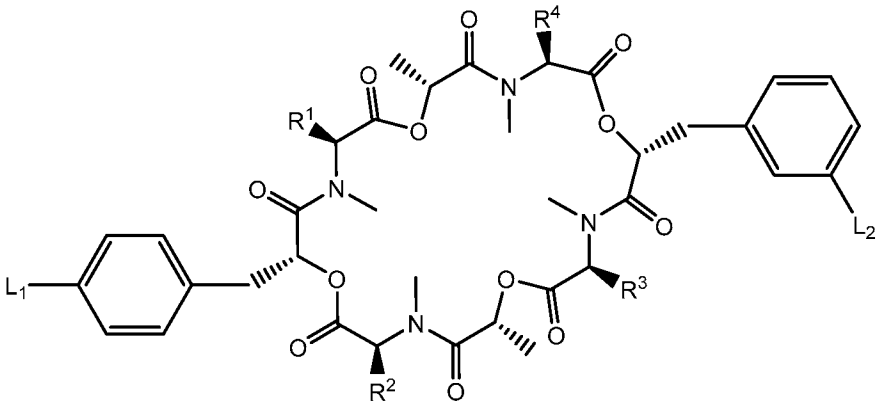
(1B1-1) or



(1B1-2)

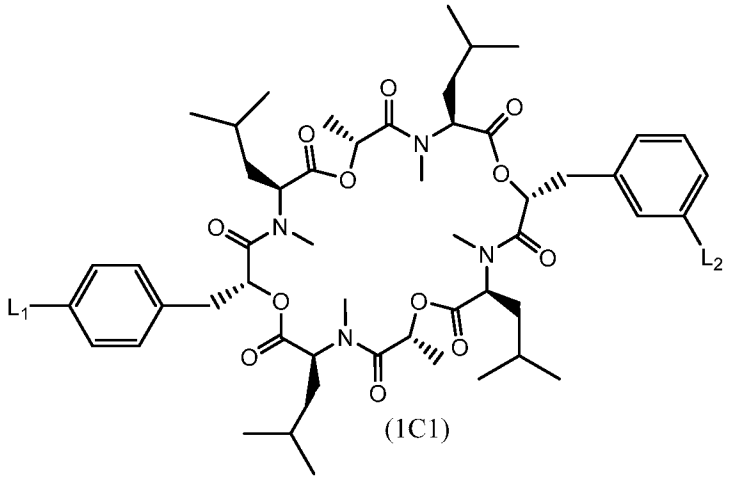
stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1B1-1) compound, stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1B1-1) selected from those compounds presented in Table 2. In yet another aspect of the invention, is a Formula (1B1-2) compound, stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1B1-2) selected from those compounds presented in Table 8. In yet another aspect of the invention, are compounds of Formula (1B1-1) presented in Table 2 and compounds of Formula (1B1-2) presented in Table 8.

In yet another aspect of the invention, is a Formula (1) compound that is a Formula (1C) compound



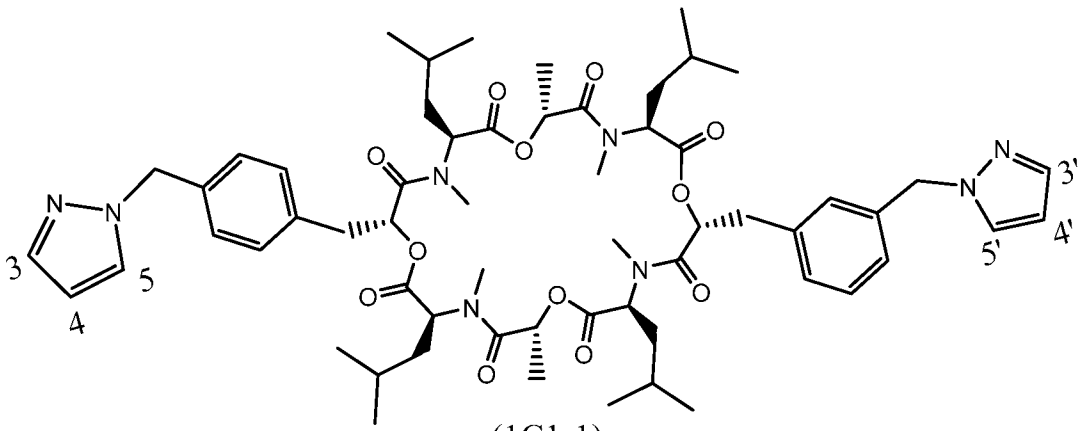
(1C)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1C) compound that is a Formula (1C1) compound

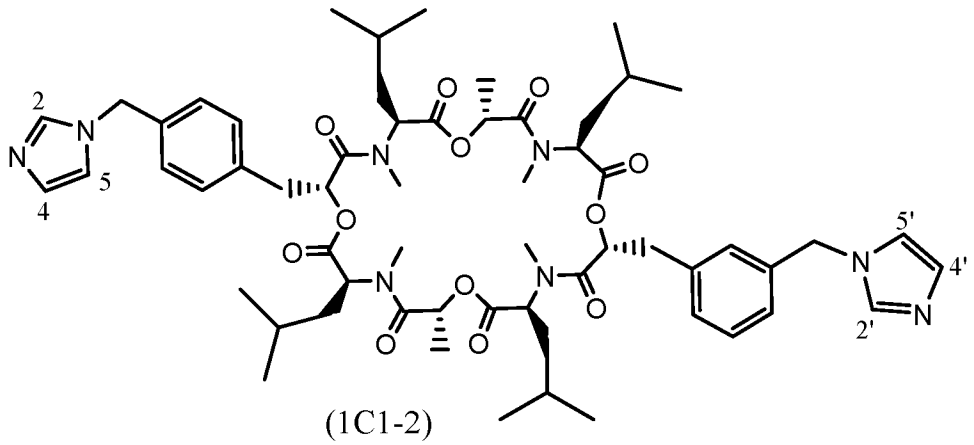


(1C1)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1C1) compound that is a Formula (1C1-1) compound or Formula (1C1-2) compound



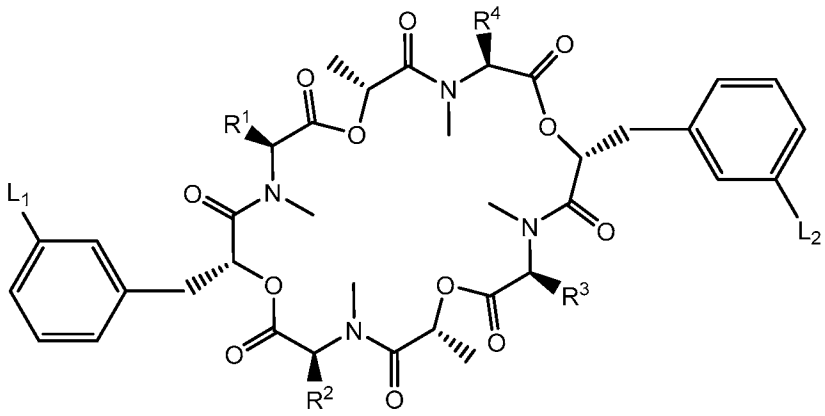
(1C1-1) or



(1C1-2)

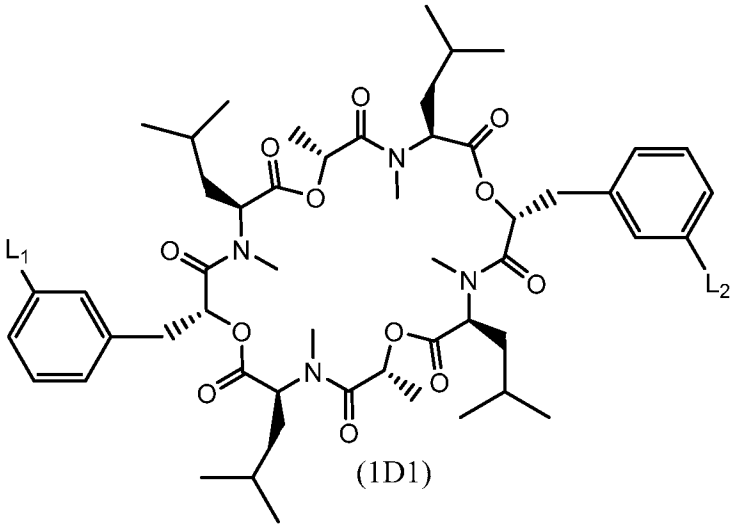
stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1C1-1) compound, stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1C1-1) selected from those compounds presented in Table 3. In yet another aspect of the invention, is a Formula (1C1-2) compound, stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1C1-2) selected from those compounds presented in Table 7.

In yet another aspect of the invention, is a Formula (1) compound that is a Formula (1D) compound



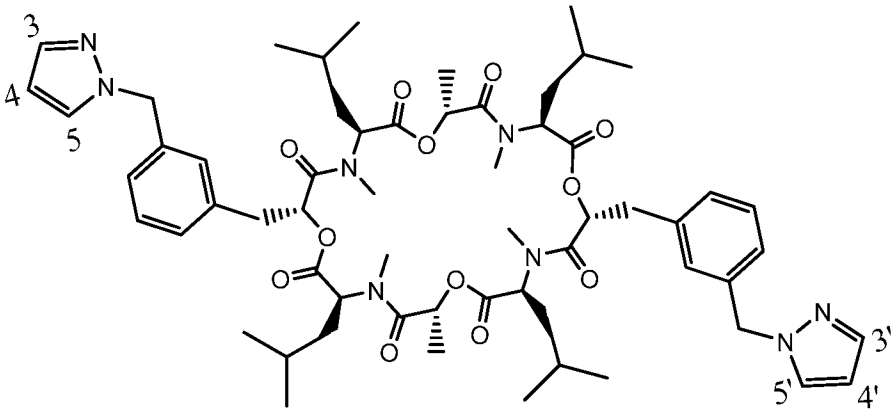
(1D)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1D) compound that is a Formula (1D1) compound



(1D1)

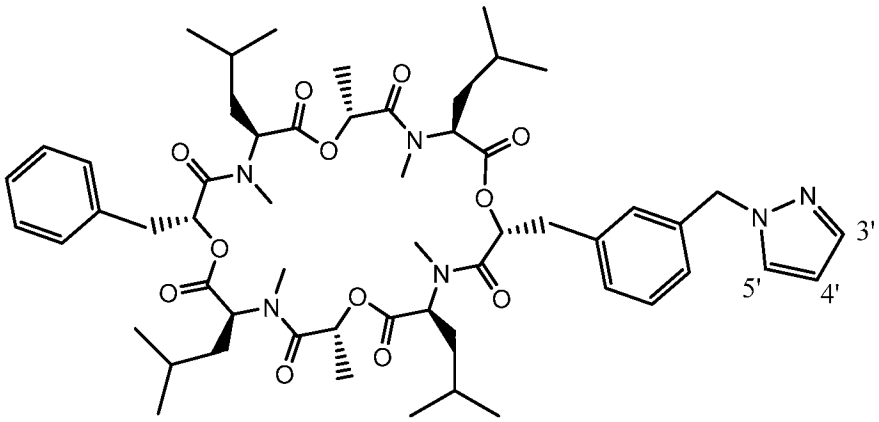
stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1D1) compound that is a Formula (1D1-1) compound



(1D1-1)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1D1-1) selected from those compounds presented in Table 4.

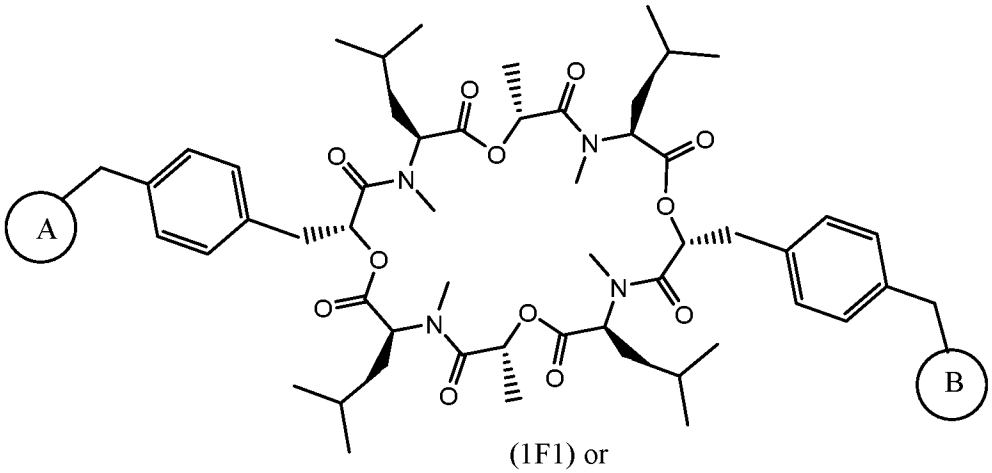
In yet another aspect of the invention, is a Formula (1) compound that is a Formula (1E1) compound



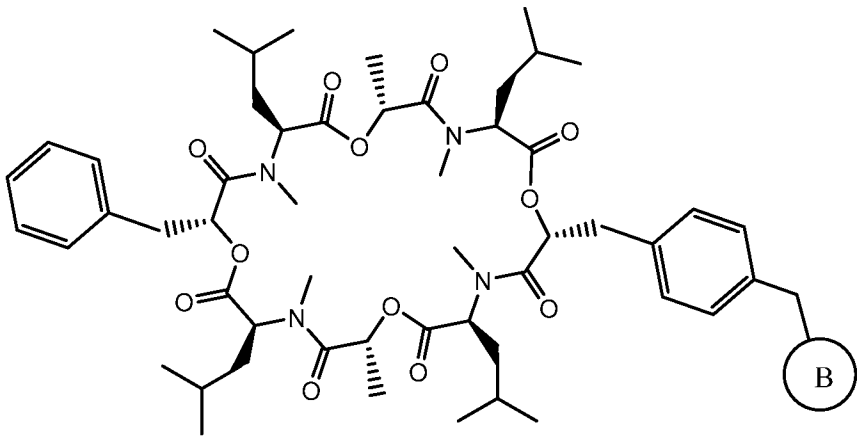
(1E1)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, are compounds of Formula (1E1) selected from those compounds presented in Table 5.

In yet another aspect of the invention, is a Formula (1) compound that is a Formula (1F1) compound or Formula (1F2) compound



(1F1) or



(1F2)

stereoisomers thereof, and veterinary acceptable salts thereof. In yet another aspect of the invention, is a Formula (1F1) compound. In yet another aspect of the invention are compounds of Formula (1F1) selected from those compounds presented in Table 9. In yet another aspect of the invention, is a Formula (1F2) compound. In yet another aspect of the invention, are compounds of Formula (1F2) selected from those compounds presented in Table 10.

In yet another aspect of the invention, are compounds that have a Minimal Effective Dose (MED) against D.immitis microfilaria (DiMF) at a value of ≤1nM and include: 1a-36, 1a-37, 1b-16, 1b-17, 1b-18, 1b-23, 1b-32, 1b-66, 1b-86, 1b-96, 1b-104, 1b-115, 1b-146, 1b-160, 1b-166, 1b-168, 1b-171, 1b-173, 1b-176, 1b-177, 1b-189, 1b-194, 1b-208, 1b-212, 1c-1, 1c-3, 1c-4, 1c-6, 1c-7, 1c-9, 1c-10, 2-1, 2-30, 6-3, 6-9, 6-15, 8-9, 9-12, 9-16, 9-32, 9-50, 9-54, 9-55, 10-13, and 10-31; each of which are respectively named herein. In yet another aspect of the invention, are compounds with a DiMF MED of >1nM and ≤ 10nM and include 1a-1, 1a-2, 1a-7, 1a-10, 1a-11, 1a-16, 1a-17, 1a-20, 1a-21, 1a-24, 1a-38, 1a-46, 1b-7, 1b-8, 1b-10, 1b-19, 1b-21, 1b-24, 1b-25, 1b-29, 1b-35, 1b-46, 1b-52, 1b-62, 1b-70, 1b-89, 1b-94, 1b-95, 1b-103, 1b-105, 1b-108, 1b-118, 1b-119, 1b-121, 1b-126, 1b-135, 1b-142, 1b-143, 1b-145, 1b-150, 1b-151, 1b-152, 1b-154, 1b-155, 1b-165, 1b-174, 1b-175, 1b-184, 1b-190, 1b-197, 1b-201, 1b-203, 1b-205, 1b-207, 1b-211, 1b-213, 1b-215, 1b-216, 1b-220, 1b-221, 1c-2, 1c-5, 1c-11, 1c-12, 2-2, 2-7, 2-10, 2-12, 2-18, 2-19, 2-22, 2-25, 2-28, 2-29, 2-39, 2-41, 2-44, 2-45, 2-46, 2-47, 2-48, 2-51, 2-55, 2-62, 2-65, 2-66, 2-69, 2-74, 2-75, 2-76, 2-77, 2-87, 3-1, 3-2, 3-3, 3-8, 3-11, 3-27, 3-36, 3-37, 3-39, 3-41, 4-1, 4-2, 4-14, 5-1, 5-2, 6-1, 6-12, 6-16, 6-19, 6-20, 7-3, 7-9, 8-3, 8-7, 8-8, 8-12, 8-13, 8-15, 9-1, 9-6, 9-11, 9-21, 9-22, 9-25, 9-28, 9-30, 9-34, 9-41, 9-48, 9-49, 9-51, 9-52, 9-53, 9-56, 10-6, 10-17, 10-30, 10-37, and 10-38; each of which are respectively named herein. In yet another aspect of the invention, are compounds with a DiMF MED value of >10 and ≤ 100nM and include: 1a-3, 1a-6, 1a-8, 1a-12, 1a-13, 1a-14, 1a-15, 1a-18, 1a-19, 1a-22, 1a-23, 1a-25, 1a-26, 1a-28, 1a-29, 1a-30, 1a-31, 1a-32, 1a-33, 1a-35, 1a-39, 1b-4, 1b-5, 1b-12, 1b-13, 1b-15, 1b-20, 1b-22, 1b-31, 1b-34, 1b-38, 1b-39, 1b-43, 1b-45, 1b-53, 1b-54, 1b-58, 1b-63, 1b-64, 1b-67, 1b-69, 1b-71, 1b-75, 1b-87, 1b-91, 1b-97, 1b-106, 1b-110, 1b-111, 1b-112, 1b-113, 1b-116, 1b-117, 1b-120, 1b-124, 1b-127, 1b-128, 1b-129, 1b-133, 1b-138, 1b-139, 1b-140, 1b-141, 1b-144, 1b-149, 1b-156, 1b-159, 1b-162, 1b-163, 1b-169, 1b-170, 1b-172, 1b-180, 1b-181, 1b-183, 1b-185, 1b-186, 1b-187, 1b-188, 1b-191, 1b-195,

1b-198, 1b-199, 1b-206, 1b-209, 1b-210, 1b-214, 1b-217, 1b-218, 1b-219, 1b-222, 2-3, 2-5, 2-8, 2-9, 2-11, 2-13, 2-14, 2-15, 2-16, 2-17, 2-20, 2-21, 2-23, 2-24, 2-26, 2-27, 2-31, 2-32, 2-35, 2-36, 2-38, 2-40, 2-42, 2-43, 2-50, 2-52, 2-54, 2-56, 2-57, 2-58, 2-59, 2-60, 2-61, 2-64, 2-67, 2-68, 2-70, 2-71, 2-72, 2-78, 2-79, 2-81, 2-82, 2-83, 2-84, 2-85, 2-86, 2-88, 3-10, 3-12, 3-13, 3-18, 3-19, 3-20, 3-21, 3-23, 3-24, 3-25, 3-29, 3-38, 3-43, 4-9, 4-15, 4-16, 4-17, 5-3, 5-4, 5-6, 6-2, 6-4, 6-5, 6-6, 6-7, 6-8, 6-10, 6-11, 6-14, 6-18, 7-1, 7-2, 7-4, 7-7, 7-11, 8-2, 8-4, 8-5, 8-6, 8-10, 8-11, 8-14, 9-2, 9-4, 9-5, 9-18, 9-20, 9-27, 9-29, 9-33, 9-35, 9-42, 9-57, 9-58, 9-59, 9-61, 9-62, 9-64, 10-2, 10-3, 10-9, 10-10, 10-11, 10-12, 10-14, 10-16, 10-18, 10-19, 10-21, 10-22, 10-23, 10-24, 10-25, 10-26, 10-27, 10-28, 10-32, 10-33, 10-35, and 10-41; each of which are respectively named herein.

In yet another aspect of the invention, are compounds that have a Minimal Effective Dose (MED) against D.immitis L4 larvae (DiL4) at a value of ≤ 0.1nM an include compounds 1a-7, 1b-15, 1b-66, 1b-89, 1b-96, 1b-115, 1b-119, 1b-154, 1b-166, 1b-171, 1b-176, 1b-177, 1b-211, 1b-216, 1c-1, 1c-2, 1c-3, 1c-6, 1c-7, 1c-8, 1c-10, 1c-11, 6-3, 6-9, 6-12, 9-12, 9-16, 9-48, and 10-31; each of which are respectively named herein. In yet another aspect of the invention, are compounds that have an MED value against DiL4 of > 0.1 to ≤ 1nM and include 1a-1, 1a-11, 1a-12, 1a-13, 1a-16, 1a-20, 1a-21, 1a-26, 1a-31, 1a-36, 1a-37, 1b-16, 1b-17, 1b-21, 1b-23, 1b-25, 1b-32, 1b-35, 1b-46, 1b-51, 1b-86, 1b-104, 1b-108, 1b-112, 1b-113, 1b-118, 1b-126, 1b-129, 1b-150, 1b-151, 1b-160, 1b-165, 1b-173, 1b-186, 1b-189, 1b-190, 1b-194, 1b-205, 1b-206, 1b-209, 1b-210, 1b-212, 1b-215, 1b-217, 1b-219, 1b-222, 1c-4, 1c-5, 1c-12, 1c-13, 2-1, 2-10, 2-22, 2-25, 2-28, 2-41, 2-51, 2-55, 2-62, 2-64, 2-66, 2-69, 2-76, 2-77, 3-1, 3-3, 3-18, 3-19, 3-27, 3-36, 3-37, 4-2, 6-15, 7-3, 7-9, 8-3, 8-9, 8-12, 8-15, 9-25, 9-26, 9-32, 9-55, 10-13, 10-30, and 10-38; each of which are respectively named herein. In yet another aspect of the invention, are compounds that have an MED value against DiL4 of >1 to ≤ 10nM and include 1a-34, 1a-38, 1a-39, 1b-14, 1b-19, 1b-68, 1b-69, 1b-127, 1b-128, 1b-143, 1b-146, 1b-147, 1b-149, 1b-152, 1b-153, 1b-155, 1b-168, 1b-172, 1b-174, 1b-175, 1b-178, 1b-181, 1b-184, 1b-187, 1b-197, 1b-201, 1b-203, 1b-207, 1b-208, 1b-220, 1b-221, 9-1, 9-22, 9-50, 9-51, 9-52, 9-53, 9-54, 9-56, 9-58, 9-61, 9-63, and 10-6; each of which are respectively named herein.

In yet another aspect of the invention, are compounds of the invention that are selectively potent against DiL4 with a DiMF/DiL4 ratio ≥ 10 to < 100 and include:

1a-1, 1a-12, 1a-13, 1a-20, 1a-26, 1a-31, 1a-34, 1b-14, 1b-35, 1b-46, 1b-69, 1b-89, 1b-96, 1b-108, 1b-113, 1b-126, 1b-127, 1b-128, 1b-129, 1b-149, 1b-151, 1b-171, 1b-172, 1b-186, 1b-206, 1b-209, 1b-215, 1b-216, 1b-217, 1b-219, 1c-5, 1c-8, 1c-10, 1c-11, 2-41, 2-55, 2-69, 3-3, 3-18, 3-19, 4-2, 6-12, 9-16, 9-61, 10-31, and 10-38; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including 1a-1, 1a-12, 1a-13, 1a-20, 1a-26, 1a-31, and 1a-34; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including 1b-14, 1b-35, 1b-46, 1b-69, 1b-89, 1b-96, 1b-108, 1b-113, 1b-126, 1b-127, 1b-128, 1b-129, 1b-149, 1b-151, 1b-171, 1b-172, 1b-186, 1b-206, 1b-209, 1b-215, 1b-216, 1b-217, and 1b-219; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including 1c-5, 1c-8, 1c-10, and 1c-11; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including 2-41, 2-55, 2-69, 3-3, 3-18, 3-19, 4-2, 6-12, 9-16, 9-61, 10-31, and 10-38; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 with a DiMF/DiL4 ratio ≥ 100 and include: 1a-7, 1b-15, 1b-51, 1b-68, 1b-112, 1b-119, 1b-153, 1b-154, 1b-178, 1b-210, 1b-222, 1c-2, 1c-3, 1c-11, 1c-13, 2-64, 9-26, 9-48, and 9-63; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including 1a-7; which is respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including: 1b-15, 1b-51, 1b-68, 1b-112, 1b-119, 1b-153, 1b-154, 1b-178, 1b-210, and 1b-222; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including: 1c-2, 1c-3, 1c-11, and 1c-13; each of which are respectively named herein. In yet another aspect of the invention, are compounds that are selectively potent against DiL4 including: 2-64, 9-26, 9-48, and 9-63; each of which are respectively named herein.

In yet another aspect of the invention, are compounds that had an MED ≤ 1μM against *H.contortus* L3 larvae including: 1b-18, 1b-23, 1b-66, 1b-89, 1b-94, 1b-96, 1b-104, 1b-108, 1b-115, 1b-151, 1b-160, 1b-165, 1b-171, 1b-173, 1b-176, 1b-177, 1b-206, 1b-211, 1b-212, 1b-215, 1b-216, 1b-217, 1b-219, 1b-222, 1c-1, 1c-2, 1c-3, 1c-4, 1c-5, 1c-6, 1c-7, 1c-9, 1c-10, 1c-11, 9-12, 9-16, 9-32, 9-48, and 9-55;

each of which are respectively named herein. In yet another aspect of the invention, are compounds that had an MED ≤1μM against *H.contortus* L3 larvae including 1b-18, 1b-23, 1b-66, 1b-89, 1b-94, 1b-96, 1b-104, 1b-108, 1b-115, 1b-151, 1b-160, 1b-165, 1b-171, 1b-173, 1b-176, 1b-177, 1b-206, 1b-211, 1b-212, 1b-215, 1b-216, 1b-217, 1b-219, and 1b-222; each of which are respectively named herein. In yet another aspect of the invention, are compounds that had an MED >1 to ≤ 10μM against *H. contortus* L3 larvae including: 1a-10, 1a-14, 1a-16, 1a-17, 1a-20, 1a-21, 1a-26, 1a-31, 1a-35, 1a-36, 1a-37, 1b-16, 1b-17, 1b-19, 1b-21, 1b-24, 1b-29, 1b-46, 1b-52, 1b-95, 1b-110, 1b-118, 1b-126, 1b-127, 1b-129, 1b-143, 1b-145, 1b-166, 1b-179, 1b-186, 1b-187, 1b-190, 1b-197, 1b-201, 1b-207, 1b-210, 1b-213, 1b-214, 1b-221, 2-1, 2-2, 2-7, 2-19, 2-22, 2-28, 2-30, 2-45, 2-51, 2-53, 2-66, 2-68, 2-69, 2-74, 2-79, 2-87, 3-1, 3-2, 3-3, 3-27, 6-3, 6-7, 6-9, 6-12, 6-20, 7-9, 8-3, 8-4, 8-6, 8-7, 8-8, 8-9, 8-13, 8-15, 9-1, 9-6, 9-11, 9-22, 9-28, 9-34, 9-41, 9-50, 9-51, 9-52, 9-53, 9-54, 9-56, 9-57, 9-59, 10-3, 10-6, 10-11, 10-13, 10-17, 10-18, 10-30, and 10-31; each of which are respectively named herein.

In yet another aspect of the invention, is a composition comprising a Formula (1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1A) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1A) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1A) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another

aspect of the invention is a composition comprising a Formula (1A) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1A1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1A1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1A1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1A1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1A1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1A1-1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1A1-1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1A1-1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent. In yet another aspect of the invention, is a composition comprising a Formula (1A1-1) compound described in Table 1b, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1A1-1) compound, described in Table 1b, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1A1-1) compound described in Table 1b, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In

yet another aspect of the invention is a composition comprising a Formula (1A1-1) compound described in Table 1b, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent. In yet another aspect of the invention, is a composition comprising a Formula (1A1-2) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1A1-2) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1A1-2) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1A1-2) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent. In yet another aspect of the invention, is a composition comprising a Formula (1A1-3) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1A1-3) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1A1-3) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1A1-3) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1B), (1C), or (1D) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1B), (1C), or (1D) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1B), (1C), or (1D) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at

least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1B), (1C), or (1D) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1B1), (1C1), (1D1), or (1E1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1B1), (1C1), (1D1), or (1E1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1B1), (1C1), (1D1) or (1E1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1B1), (1C1), (1D1), or (1E1) compound , stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1B1-1), (1C1-1), or (1D1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1B1-1), (1C1-1), or (1D1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1B1-1), (1C1-1), or (1D1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1B1-1), (1C1-1), or (1D1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1B1-2) or (1C1-2) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1B1-2) or (1C1-2) compound, stereoisomer thereof, and veterinary

acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1B1-2) or (1C1-2) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1B1-2) or (1C1-2) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a composition comprising a Formula (1E1), (1F1) or (1F2) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention is a composition comprising a Formula (1E1), (1F1) or (1F2) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient. In yet another aspect of the invention is a composition comprising a Formula (1E1), (1F1) or (1F2) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient, and optionally, at least one additional antiparasitic agent. In yet another aspect of the invention is a composition comprising a Formula (1E1), (1F1) or (1F2) compound, stereoisomer thereof, and veterinary acceptable salt thereof, and further comprising a veterinary acceptable excipient and at least one additional antiparasitic agent.

In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1-1)

compound described in Table 1a, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1-1) compound described in Table 1b, stereoisomer thereof, and veterinary acceptable salt thereof.

In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1-2) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1-3) compound, stereoisomer thereof, and veterinary acceptable salt thereof.

In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1B) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1B1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1B1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1B1-2) compound, stereoisomer thereof, and veterinary acceptable salt thereof.

In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1C) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1C1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1C1-1) compound, stereoisomer thereof, and veterinary acceptable salt

thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1C1-2) compound, stereoisomer thereof, and veterinary acceptable salt thereof.

In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1D) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1D1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1D1-1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1E1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1F1) compound, stereoisomer thereof, and veterinary acceptable salt thereof. In yet another aspect of the invention, is a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1F2) compound, stereoisomer thereof, and veterinary acceptable salt thereof.

In another aspect of the invention, the method of treating a parasitic infection in an animal in need thereof which comprises administering an effective amount of a Formula (1), Formula (1A), Formula (1A1), Formula (1A1-1), Formula (1A1-2), Formula (1A1-3), Formula (1B), Formula (1B1), Formula (1B1-1), Formula (1B1-2), Formula (1C), Formula (1C1), Formula (1C1-1), Formula (1C1-2), Formula (1D), Formula (1D1), Formula (1D1-1), Formula (1E1), Formula (1F1), or Formula (1F2) compound. In another aspect of the invention, the method of treating a parasitic infection in an animal in need thereof which comprises administering an effective amount of a compound of Formula (1A1), Formula (1A1-1), or Formula (1A1-2). In another aspect of the invention, the method of treating a parasitic infection in an animal in need thereof which comprises administering an effective amount of a

compound of Formula (1A1-1). In another aspect of the invention, the method of treating a parasitic infection in an animal in need thereof which comprises administering an effective amount of a compound of Formula (1A1-1) described in Table 1a. In another aspect of the invention, the method of treating a parasitic infection in an animal in need thereof which comprises administering an effective amount of a compound of Formula (1A1-1) described in Table 1b. In another aspect of the invention, the method of treating a parasitic infection in an animal in need thereof which comprises administering an effective amount of a compound of Formula (1A1-2). In another aspect of the invention, the method of treating a parasitic infection in an animal in need thereof which comprises administering an effective amount of a compound of Formula (1F1). The term “administering”, as described above, includes oral, topical, and injectable means. Injectable includes subcutaneous, intramuscular, and intravenous injection. The term “animal”, as described above, includes companion animals. Preferred, companion animal refers to canine. The term “parasitic infection”, as described above, refers to an endoparasitic infection, preferably an endoparasitic infection caused by a filarial parasite. In certain aspects, the filarial parasite is Dirofilaria immitis (heartworm).

In yet another aspect of the invention, is the use of a Formula (1), Formula (1A), Formula (1A1), Formula (1A1-1), Formula (1A1-1; Table 1a), Formula (1A1-1; Table 1b), Formula (1A1-2), Formula (1A1-3), Formula (1B), Formula (1B1), Formula (1B1-1), Formula (1B1-2), Formula (1C), Formula (1C1), Formula (1C1-1), Formula (1C1-2), Formula (1D), Formula (1D1), Formula (1D1-1), Formula (1E1), Formula (1F1), or Formula (1F2) compound to treat a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A), Formula (1A1), Formula (1A1-1), Formula (1A1-1; Table 1a), Formula (1A1-1; Table 1b), Formula (1A1-2), or Formula (1F1) compound to treat a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A1) compound to treat a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A1-1) compound to treat a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A1-1) compound described in Table 1a to treat a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A1-1) compound described in Table 1b to treat a parasitic infection in an animal in need thereof. In yet another aspect of the

invention, is the use of a Formula (1A1-2) compound to treat a parasitic infection in an animal in need thereof.

In yet another aspect of the invention, is the use of a Formula (1), Formula (1A), Formula (1A1), Formula (1A1-1), Formula (1A1-1; Table 1a), Formula (1A1-1; Table 1b), Formula (1A1-2), Formula (1A1-3), Formula (1B), Formula (1B1), Formula (1B1-1), Formula (1B1-2), Formula (1C), Formula (1C1), Formula (1C1-1), Formula (1C1-2), Formula (1D), Formula (1D1), Formula (1D1-1), Formula (1E1), Formula (1F1), or Formula (1F2) compound to prepare a medicament for treating a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A), Formula (1A1), Formula (1A1-1), Formula (1A1-1; Table 1a), Formula (1A1-1; Table 1b), Formula (1A1-2), or Formula (1F1) compound to prepare a medicament for treating a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A1) compound to prepare a medicament for treating a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A1-1) compound to prepare a medicament for treating a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1A1-1) compound described in Table 1a to prepare a medicament for treating a parasitic infection in an animal in need thereof. . In yet another aspect of the invention, is the use of a Formula (1A1-1) compound described in Table 1b to prepare a medicament for treating a parasitic infection in an animal in need thereof.

In yet another aspect of the invention, is the use of a Formula (1A1-2) compound to prepare a medicament for treating a parasitic infection in an animal in need thereof. In yet another aspect of the invention, is the use of a Formula (1F1) compound to prepare a medicament for treating a parasitic infection in an animal in need thereof.

The compounds of the invention are intended to encompass racemic mixtures, specific stereoisomers, regional-isomers, and tautomeric forms of the compound

DETAILED DESCRIPTION

Definitions

For purposes of the present invention, as described and claimed herein, the following terms and phrases are defined as follows:

“Additional veterinary agent(s)” as used herein, refers to other veterinary or veterinary compounds or products that provide a therapeutically effective amount of said agents that are useful for the treatment of a parasitic infection in an animal, as described herein.

“Alkoxy”, as used herein, refers to alkyl-O-, wherein the term alkyl is defined below. Non-limiting alkoxy examples include: methoy, ethoxy, propoxy, isopropoxy, n-butoxy, n-pentoxy, 1-methylbutoxy, 1-ethylpropoxy, and the like.

"Alkyl", as used herein, unless otherwise indicated, refers to saturated monovalent hydrocarbon alkane radicals of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched and may be unsubstituted or substituted. For example, the term “(C_1-C_6)alkyl” refers to a monovalent, straight or branched aliphatic group containing 1 to 6 carbon atoms. Non-exclusive examples of (C_1-C_6) alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, sec-butyl, t-butyl, n-propyl, n-butyl, i-butyl, s-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, 2-methylpentyl, hexyl, and the like. The alkyl moiety may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Alkyls are optionally substituted as described herein.

“Alkenyl” as used herein, unless otherwise indicated, refers to a straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon double bond (for example -C=C-). Non- exclusive examples of alkenyl include: ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-pentenyl, and the like. Alkenyls are optionally substituted as described herein.

“Alkynyl” as used herein, unless otherwise indicated, refers to straight or branched aliphatic hydrocarbon chain having 2- to 6-carbon atoms and containing at least one carbon-carbon triple bond (for example, -C≡C- or -C≡CH). Non- exclusive examples of alkynyl include: ethynyl, 2-propynyl, 1-methyl-2-propynyl, 2-butynyl, 3-butynyl, 2-methyl-3-butynyl, and the like. Alkynyls are optionally substituted as described herein.

“Animal(s)”, as used herein, unless otherwise indicated, refers to an individual animal that is a mammal or bird. Specifically, mammal refers to a vertebrate animal that is human and non-human, which are members of the taxonomic class Mammalia. Non-exclusive examples of non-human mammals include companion animals and livestock. Non-exclusive examples of a companion animal include: dog,

cat, llama, and horse. Preferred companion animals are dog, cat, and horse. More preferred is dog. Non-exclusive examples of livestock include: swine, camel, rabbits, goat, sheep, deer, elk, bovine (cattle), and bison. Preferred livestock is cattle and swine. Specifically, bird refers to a vertebrate animal of the taxonomic class Aves. Birds are feathered, winged, bipedal, endothermic, and egg-laying. Non-exclusive examples of bird include, poultry (e.g., chicken, turkey, duck, and geese), all of which are also referred to herein as fowl.

"Aryl", as described herein, refers to a monovalent aromatic carbocyclic group of from 6 to 10 carbon atoms having a single ring or multiple fused rings. Aryl groups include, but are not limited to, phenyl, biphenyl, and naphthyl. Aryls are optionally substituted as described herein.

“Chiral”, as used herein, unless otherwise indicated, refers to the structural characteristic of a molecule that makes it impossible to superimpose it on its mirror image, (e.g., “R” and “S” enantiomers).

“Comprise(s)”, as used herein, refers to an inclusive meaning, i.e., that it will be taken to mean an inclusion of not only the listed components it directly references, but also other non-specified components or elements. This rationale will also be used when the term “comprised” or “comprising” is used in relation to one or more Steps in a method or process. Contains is herein construed as being synonymous to comprise. The term “consisting of”, and/or “consisting essentially of” has a non-inclusive meaning.

“Compounds of the present invention", as used herein, unless otherwise indicated, refers to compounds of Formula (1), stereoisomers thereof, and veterinary acceptable salts thereof. The term and/or phrase also refer to the sub-genus formulas of Formula (1) including: Formula (1A1), Formula (1A1-1), Formula (1A1-2), Formula (1B1), Formula (1B1-1), Formula (IB1-2), Formula (1C1), Formula (1C1-1), Formula (1C1-2), Formula (1D1), Formula (1D1-1), Formula (1E1), and Formula (1E2), stereoisomers thereof, and vetertinary acceptable salts thereof. Synonomously, the compounds of thepresent invention are described as depsipeptide(s) and octadepsipeptide(s).

"Cycloalkyl", as used herein, unless otherwise indicated, includes fully saturated or partially saturated carbocyclic alkyl moieties. Non-limiting examples of partially saturated cycloalkyls include: cyclopropene, cyclobutene, cycloheptene, cyclooctene, cyclohepta-1,3-diene, and the like. Preferred cycloalkyls are 3- to 6-

membered saturated monocyclic rings including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The cycloalkyl group may be attached to the chemical moiety by any one of the carbon atoms within the carbocyclic ring. Cycloalkyl groups are optionally substituted as described herein.

“Halogen" or “halo”, as used herein, unless otherwise indicated, refers to fluorine, chlorine, bromine and iodine. Further, when used in compound words such as "haloalkyl", “haloalkoxy”, “haloalkenyl”, or “haloalkynyl”, said alkyl, alkoxy, alkenyl, and alkynyl may be partially or fully substituted with halogen atoms which may be the same or different and said alkyl, alkoxy, alkenyl, and alkynyl moiety has the same meaning as above and may be attached to the chemical moiety by any one of the carbon atoms of the aliphatic chain. Examples of haloalkyl include F_3C-, F_2CH-$ClCH_2$-, CF_3CH_2- and CF_2CCl_2-, and the like. The term "haloalkoxy" is defined analogously to the term "haloalkyl". Examples of haloalkoxy include CF_3O-, CCl_3CH_2O-, $HCF_2CH_2CH_2O$- and CF_3CH_2O-, and the like.

“Het”, as used herein, unless otherwise indicated, refers to heteroaryl or heterocycle; each as described herein.

“Heteroaryl”, as used herein, unless otherwise indicated, refers to a 5- to 6-membered aromatic monocyclic ring or an 8- to 11-membered fused aromatic ring where said monocyclic- and fused-ring moiety contains one or more heteroatoms each independently selected from N, O, or S, preferably from one to four heteroatoms. Non-exclusive examples of monocyclic heteroaryls include pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, and the like. Preferred monocyclic heteroaryls include pyrazole, imidazole, and triazole. More preferred monocyclic heteroaryls are pyrazoles and imidazoles. A more preferred monocyclic heteroaryl is pyrazole. A more preferred monocyclic heteroaryl is imidazole. Non-exclusive examples of fused heteroaryls include: benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl (e.g.,1H-benzo[d]imidazole), indazolyl, pyrrolopyrazolyl (e.g., 5,6-dihydropyrrolo[3,4-c]pyrazole, 6,7-dihydropyrano[4,3-c]pyrazole, 5,6-dihydropyrrolo[3,4-c]pyrazole), benzoxazines (e.g., 2,3-dihydro-4H-benzo[b][1,4]oxazine), benzothiazines (e.g., 2,3-dihydro-4H-benzo[b][1,4]thiazine), pyridooxazines (e.g., 2,3-dihydropyrido[2,3-b][1,4]oxazine, 2,3-dihydropyrido[4,3-b][1,4]oxazine, 2,3-dihydropyrido[3,2-b][1,4]oxazine), pyridothiazines (e.g., 2,3-dihydropyrido[2,3-b][1,4]thiazine, pyrido[3,2-b][1,4]thiazine), quinoxalines (e.g., 2,3-

dihydroquinoxaline, 3,4-dihydro-2H-quinoxaline), quinolinyl, benzotriazolyl (e.g.,1H-benzo[d][1,2,3]triazole), thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, benzo[1,2,5]thiadiazole, pyrrolopyridine (e.g., 1H-pyrrolo[2,3-b]pyridine; 1H-pyrrolo[2,3-c]pyridine), tetrahydrocyclopentalpyrazole (e.g.,1,4,5,6-tetrahydrocyclopenta[c]pyrazole, 2,4,5,6-tetrahydrocyclopenta[c]pyrazole), 5,6-dihydrocyclopenta[c]pyrazole, 1H-pyrazolo[3,4-b]pyridine, and the like. The heteroaryl ring is attached to the chemical moiety by any one of the nitrogen heteroatoms within the monocyclic or fused ring. Heteroaryls are optionally substituted as described herein.

"Heterocycle", as used herein, unless otherwise indicated, refers to a partially saturated or saturated 4- to 6-membered monocyclic ring, 8- to 11-membered fused ring, each containing one or more heteroatoms independently selected from N, O, or S, preferably from one to four heteroatoms. Non-exclusive examples of heterocycle include oxirane, thiarane, aziridine, oxetane, azetidine, thiatane, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, morpholine, thiomorpholine, tetrahydropyrane, piperidine, piperazine, tetrahydropyridine, 2H-azirine, 2,3-dihydro-azete, 3,4-dihydro-2H-pyrrole, azathiane, oxazinane, imidazolidine, oxazolidine, isoxazolidine, 1,2-dihydropyridine, and the like. The heterocyclic ring is attached to the chemical moiety by any one of the nitrogen heteroatoms within the moncyclic or fused ring. Heterocycles are optionally substituted as described herein.

"Optionally substituted", is used herein interchangeably with the phrase substituted or unsubstituted. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other. An optionally substituted group also may have no substituents. Therefore, the phrase "optionally substituted with at least one substituent" means that the number of substituents may vary from zero up to a number of available positions for substitution.

"Parasite(s)", as used herein, unless otherwise indicated, refers to endoparasites and ectoparasites. Endoparasites are parasites that live within the body of its host and include helminths (e.g., trematodes, cestodes, and nematodes) and protozoa. Ectoparasites are organisms of the Arthropoda phylum (e.g., arachnids, insects, and crustaceans (e.g., copepods-sea lice) which feed through or upon the skin of its host. Preferred arachnids are of the order Acarina, e.g., ticks and mites. Preferred insects are midges, fleas, mosquitos, biting flies (stable fly,

horn fly, blow fly, horse fly, and the like), bed bugs, and lice. Preferred compounds of the present invention can be used for the treatment of parasites, i.e., treatment of a parasitic infection or infestation.

“Percent” (%), as used herein, refers to individual percent values. When referring to % in liquids (volume/volume% or v/v%) like an aqueous organic solvent, the % is the volume % of the solvent in the total volume of the solution. When referring to % for solids in liquids (weight/volume% or w/v%), the % value is construed to be the weight of the solid in the total volume of the solution and refers to the number of grams of solute in 100mL of solution. When referring to solids (weight% or w/w%) refers to the weight (mass) of one component relative to the total weight (mass) of the solid composition.

“Protecting group” or “Pg”, as used herein, unless otherwise indicated, refers to a substituent that is commonly employed to block or protect an amine on the compound thereby protecting its functionality while allowing for the reaction of other functional groups on the compound. Non-exclusive examples of an amine-protecting group include: acyl groups (e.g., formyl, acetyl, chloroacetyl, trichloro-acetyl, *o*-nitrophenylacetyl, *o*-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, *o*-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl, and the like), acyloxy groups (e.g., 1-*tert*-butyloxycarbonyl (Boc), methoxycarbonyl, 9-fluorenyl-methoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethxoycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, 1,1 –dimethyl-propynyloxycarbonyl, benzyloxy-carbonyl, p-nitrobenzyloxycarbony, 2,4-dichlorobenzyloxycarbonyl, and the like), diphenylmethane, and benzylcarbamates.

“Substituted”, as used herein, refers to a substituent that is bonded to the chemical moiety in place of a hydrogen atom. Common substituents of the invention for alkyl, cycloalkyl, aryl, heterocyle, heteroaryl moieties, an d the like, are as described herein, and include, for example, $-NO_2$, -CN, alkyl, halo, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, hydroxy, amino, alkylamino, dialkylamino, and the like. Substituents can be bonded to any carbon in the aliphatic chain or carbocyclic, aryl, heterocyclic, or heteroaryl ring system. The substituent can also be bonded to any accepting nitrogen and/or sulfur atom.

"Therapeutically effective amount", as used herein, refers to an amount of the active agent (i.e., Formula (1) compound) that (i) treat the particular parasitic infection or infestation, (ii) attenuates, ameliorates, or eliminates one or more

symptoms of the particular parasitic infection or infestation, or (iii) prevents or delays the onset of one or more symptoms of the particular parasitic infection or infestation described herein. The active agent may be in a composition sufficient to elicit the desired biological response to the target parasite(s) after administration of the composition to the animal, as measured by methods known in the art and/or described in the examples herein. In some instances, an "effective amount" of the active agent in the composition will provide an efficacy of at least 70% against the target parasite compared to an untreated control. In other instances, "an effective amount" of the active agent will provide an efficacy of at least 80%, or at least 85% compared to untreated controls. More typically, "an effective amount" of the active agent will provide an efficacy of at least 90%, at least 93%, at least 95% or at least 97% against the target parasite. In certain instances, including the prevention of Dirofilaria immitis, the term "effective amount" may provide efficacy as high as 100%. As is understood in the art, a therapeutically effective amount may be in one or more doses, i.e., a single dose or multiple doses may be required to achieve the desired treatment endpoint, for example, (i) treat the particular parasitic infection or infestation, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular parasitic infection or infestation, or (iii) prevents or delays the onset of one or more symptoms of the particular parasitic infection or infestation described herein. The therapeutically effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

"Treatment", "treating", and the like, as used herein, unless otherwise indicated, refers to reversing, alleviating, or inhibiting the parasitic infection, infestation, or condition. As used herein, these terms also encompass, depending on the condition of the animal, preventing the onset of a disorder or condition, or of symptoms associated with a disorder or condition, including reducing the severity of a disorder or condition or symptoms associated therewith prior to affliction with said infection or infestation or after said infection or infestation. Thus, treatment can refer to administration of the compounds of the present invention to an animal that is not at the time of administration afflicted with the infection or infestation. Treating also encompasses preventing the recurrence of an infection or infestation or of symptoms associated therewith as well as references to “control” (e.g., kill, repel, expel, incapacitate, deter, eliminate, alleviate, minimize, and eradicate).

"Veterinary acceptable" as used herein, unless otherwise indicated, indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, composition, and/or the animal being treated therewith.

The Formula (1) compounds of the invention are 24-membered cyclic depsipeptide compounds which have potent activity against endoparasites such as nematodes and filarial worms (microfilarial and larval stages) and also in some cases against ectoparasites such as fleas and ticks. In one aspect of the invention is a cyclic depsipeptide of Formula (1), or a veterinaryly acceptable salt thereof. Surprisingly, it has been found that addition of a methylene linker between the aryl ring in one or both of the phenyl lactate groups in the molecule versus the parent cyclic depsipeptide PF1022 and emodepside, improves the selectivity and activity of the compounds against parasites, particularly, endoparasites. This improvement provides selectivity against the L3 and L4 larvae and the actual microfilaria by killing the L3 and L4 larvae before metamorphosis into the next lifecycle change, the animal is healthier and does not need to succumb to the killing of microfilaria or adult worms which can cause emboli and ultimately death to the host animal. Furthermore, it has been surprisingly found that substitution of the compounds of Formula (1) with certain L1 and L2 groups also significantly improves the in vitro metabolic stability of the compounds of the invention compared with PF1022 and emodepside. Thus, the compounds of the invention have been found to have significantly improved metabolic stability and equal or significantly improved efficacy against endoparasites including Dirofilaria immitis microfilaria and/or L3 and L4 larvae and/or Haemonchus contortus larvae. In some aspects, the compounds of Formula (1) with certain substituents will also exhibit improved activity against ectoparasites.

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, "Reagents for Organic Synthesis", 1; 19, Wiley, New York (1967, 1999 ed.), or

Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)). For illustrative purposes, the reaction schemes depicted below demonstrate potential routes for synthesizing compounds of the present invention, and key intermediates. For a more detailed description of the individual reaction Steps, see the Examples section below. A skilled artisan will appreciate that other suitable starting materials, reagents, and synthetic routes may be used to synthesize the compounds of the present invention and a variety of derivatives thereof. Further, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to the skilled artisan.

The depsipeptides of the present invention described herein, include one or more chiral centers which results in a theoretical number of optically active isomers. Where compounds of the invention include n chiral centers, the compounds may comprise up to 2n optical isomers. The present invention encompasses the specific enantiomers or diastereomers, and mixtures thereof, of each compound. The optically active forms can be prepared by, for example, resolution of the racemic forms by selective crystallization techniques, by synthesis from optically active precursors, by chiral synthesis, by chromatographic separation using a chiral stationary phase or by enzymatic resolution. The depsipeptides of the present invention include their respective stereoisomers.

For illustrative purposes, the reaction schemes depicted below demonstrate potential routes for synthesizing key intermediates and compounds of the present invention. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other suitable starting materials, reagents, and synthetic routes may be used to synthesize the intermediates and compounds of the present invention and a variety of derivatives thereof. Further, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry. Schemes 1-3 outline the general procedures useful for the preparation and isolation of compounds of the present invention. It is to be understood, however, that the invention, as fully described herein and as recited in the claims, is not intended to be limited by the details of the following schemes or modes of preparation. In the preparation of compounds of the present invention, protection of remote functionality

of intermediates from undesired reactions can be accomplished with a protecting group.

In the preparation of compounds of the present invention, protection of remote functionality of intermediates from undesired reactions can be accomplished with a protecting group. The term “protecting group” or “Pg” refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an amine-protecting group is a substituent attached to an amine that blocks or protects the amine-functionality of the compound or intermediate. Suitable amine protecting groups include: 1-*tert*-butyloxycarbonyl (Boc), acyl groups including: formyl, acetyl, chloroacetyl, trichloro-acetyl, *o*-nitrophenylacetyl, *o*-nitrophenoxyacetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, *o*-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl, and the like; and acyloxy groups including: methoxycarbonyl, 9-fluorenyl-methoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethxoycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, 1,1 –dimethyl-propynyloxycarbonyl, benzyloxy-carbonyl, p-nitrobenzyloxycarbony, 2,4-dichlorobenzyloxycarbonyl, and the like. Similarly, diphenylmethane and benzylcarbamates can be used as amine protecting groups. Suitable protecting groups and their respective uses are readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

The compounds of the invention are intended to encompass racemic mixtures, specific stereoisomers and tautomeric forms of the compound. Another aspect of the invention is a salt form of the compound of the invention.

The compounds of present invention may also be present in different solid forms such as different crystalline forms or in the form of an amorphous solid. The present invention encompasses different crystalline forms as well as amorphous forms of the inventive compounds.

In addition, the compounds of the invention may exist as hydrates or solvates, in which a certain stoichiometric amount of water or a solvent is associated with the molecule in the crystalline form. The hydrates and solvates of the compounds of formula (I) are also the subject of the invention.

In addition to the neutral compounds of Formula (1), salt forms of the compounds are also active against endoparasites. The term "veterinary acceptable salt" is used throughout the specification to describe any salts of the compounds that are acceptable for administration for veterinary applications, and which provides the active compound upon administration.

In cases where compounds are sufficiently basic or acidic to form stable non-toxic acid or base salts, the compounds may be in the form of a veterinary or agriculturally acceptable salt. Veterinary acceptable salts include those derived from veterinary or agriculturally acceptable inorganic or organic bases and acids. Suitable salts include those comprising alkali metals such as lithium, sodium or potassium, alkaline earth metals such as calcium, magnesium and barium. Salts comprising transition metals including, but not limited to, manganese, copper, zinc and iron are also suitable. In addition, salts comprising ammonium cations (NH_4^+) as well as substituted ammonium cations, in which one or more of the hydrogen atoms are replaced by alkyl or aryl groups are encompassed by the invention.

Salts derived from inorganic acids including, but not limited to, hydrohalide acids (HCl, HBr, HF, HI), sulfuric acid, nitric acid, phosphoric acid, and the like are particularly suitable. Suitable inorganic salts also include, but not limited to, bicarbonate, and carbonate salts. In some embodiments, examples of veterinary and agriculturally acceptable salts are organic acid addition salts formed with organic acids including, but not limited to, maleate, dimaleate, fumarate, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, a-ketoglutarate, and a-glycerophosphate. Of course, other acceptable organic acids may be used.

Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of the compounds can also be made by reacting a sufficiently acidic residue on the compounds with a hydroxide of the alkali metal or alkaline earth metal.

Veterinaryly acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitably acid functional group present in the compound, or by

reacting a suitable acid with a suitably basic functional group on the compound of the invention.

The compounds of Formula (1) may be prepared by processes adapted from those described in US Patent Nos. 5,514,773; 5,747,448; 5,874,530; 5,856,436; 6,033,879; 5,763,221; 6,329,338, 5,116,815; 6,468,966; 6,369,028; 5,777,075; and 5,646,244. In addition, various synthetic methods for cyclic depsipeptides have been reported in the chemical literature (see Luttenberg *et al., Tetrahedron* 68 (2012), 2068-2073; Byung H. Lee, *Tetrahedron Letters,* 1997, 38 (5), 757-760; Scherkenbeck *et al., Eur. J Org. Chem.,* 2012, 1546-1553; *Biosci. Biotech. Biochem.,* 1994, 58(6), 1193-1194; and Scherkenbeck *et al., Tetrahedron,* 1995, 51(31), 8459-8470) It will be understood by those skilled in the art that certain functional groups in the compounds and intermediates may be unprotected or protected by suitable protecting groups, as taught by Greene and Wuts, *Protective Groups in Organic Synthesis,* John Wiley and Sons, Inc., 4th edition 2006. Further, it will be apparent to those skilled in the art that the compounds and intermediates may be isolated by standard aqueous work-up conditions and optionally purified. For example, the compounds or intermediates may be purified by chromatographic methods or crystallized to yield the desired product in suitable purity.

One skilled in the art will recognize that, in some cases, after the introduction of a given reagent as it is depicted in the schemes, it may be necessary to perform additional routine synthetic Steps not described in detail to complete the synthesis of Formula (1) compounds.

The present invention includes all veterinary acceptable isotopically-labelled Formula (1) compounds wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the present invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, and sulphur, such as ^{35}S.

The skilled person will appreciate that the compounds of the present invention could be made by methods other than those herein described as incorporated herein by reference, by adaptation of the methods herein described and/or adaptation of

methods known in the art, for example the art described herein, or using standard textbooks such as "Comprehensive Organic Transformations - A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 or later editions).

The Formula (1) compounds are useful as antiparasitic agents, therefore, another aspect of the present invention is a veterinary composition comprising a therapeutically effective amount of a Formula (1) compound, stereoisomers thereof, and at least one veterinary acceptable excipient. The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

The compound of the present invention can be administered alone or in a formulation appropriate to the specific use envisaged, the particular species of host animal being treated and the parasite involved. Generally, it will be administered as a formulation in association with at least one veterinary acceptable excipient. The term “excipient” is used herein to describe any ingredient (e.g., carrier, diluents, and the like) other than the compound of the present invention or any additional veterinary (*e.g.*, antiparasitic) agent. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. In addition to the excipient(s), the amount of the compound of the present invention that is administered and the dosage regimen for treating a condition or disorder with the compound depends on a variety of factors, including the age, weight, sex and medical condition of the animal, the severity of the disease, the route and frequency of administration, and thus may vary widely.

In another aspect, the veterinary composition comprises a Formula (1) compound with at least one veterinary acceptable excipient. The concentration range will vary depending on the composition (e.g., oral, topical, or injectable). For an oral dose, the range of active (i.e., compound of the present invention) is about 0.1 to 50 mg/kg, preferably from about 0.2 to 25 mg/kg, and even more preferably from about 0.25 to 10mg/kg, and most preferably from about 0.5 to 7 mg/kg or 1-5 mg/kg. For a topical solution, the range of active is about 0.1 to 1000 mg/mL, and preferably from about 0.5 to 500 mg/mL, and more preferably from about 1 to 250 mg/mL, and even more preferably from about 2 to 200 mg/mL. Depending upon the final volumes of the topical solution(s), the concentration of the active can change

from that described above. Generally, injectable doses tend to be, but not always, lower in concentration.

The formulations can be prepared using conventional dissolution and mixing procedures. Such compositions and methods for their preparation may be found, for example, in 'Remington's Veterinary Sciences', 19th Edition (Mack Publishing Company, 1995; and "Veterinary Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., 1980 (ISBN 0-8247-6918-X).

A typical formulation is prepared by mixing a Formula (1) compound with at least one veterinary acceptable excipient. Suitable excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, starches, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular excipient(s) will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe to be administered to an animal. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or veterinary composition thereof) or aid in the manufacturing of the veterinary product (i.e., medicament). The compound of the present invention will typically be formulated into veterinary dosage forms to provide an easily controllable dosage form for administration.

The methods by which the compound of the present invention may be administered include oral, topical, and injectable (e.g., parenteral and subcutaneous) administration. The particular route selected by the practitioner depends upon factors such as the physicochemical properties of the therapeutic agent, the condition of the host and economics. In certain cases, it is convenient and efficient to administer veterinary medicines orally by placing the therapeutic agent in a solid or liquid matrix that is suitable for oral delivery. These methods include chewable drug-delivery formulations. The problem associated with administering oral formulations to animals is that the therapeutic agent often provides an unpleasant taste, aroma, or texture, which causes the animals to reject the composition. This is further exacerbated by compositions that are hard and difficult to swallow.

The compound of the present invention can be administered orally by capsule, bolus, tablet, powders, lozenges, chews, multi and nanoparticulates, gels, solid solution, films, sprays, or liquid form. This is a preferred method of administration and as such it is desirable to develop the compound for oral administration. Such formulations may be employed as fillers in soft or hard capsules, soft or hard palatable chews, which typically comprise at least one veterinary acceptable excipient, for example, water, ethanol, polyethylene glycol, N-methylpyrrolidone, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents, flavorants, and/or suspending agents. Liquid forms include suspensions, solutions, syrups, drenches and elixirs. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. Oral drenches are commonly prepared by dissolving or suspending the compound of the present invention in a suitable medium (e.g. triethylene glycol, benzyl alcohol, and the like). The compound of the present invention can also be formulated with a food substance, e.g., a dietary admixture (food pellets or powder for birds).

The compound of the present invention can be administered topically to the skin or mucosa, that is dermally or transdermally. This is another preferred method of administration and as such it is desirable to develop the compound of the present invention to be suited to such formulations, for example liquid forms. Typical formulations for this purpose include pour-on, spot-on, multi-spot-on, stripe-on, comb-on, roll-on, dip, spray, mousse, shampoo, powder formulation, gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and micro emulsions. Liposomes may also be used. Typical excipients include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, N-methyl formamide, glycol monomethyl ethers, polyethylene glycol, propylene glycol, and the like. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Pour-on or spot-on formulations may be prepared by dissolving the active ingredients in an acceptable liquid excipient such as butyl digol, liquid paraffin or a non-volatile ester, optionally with the addition of a volatile component such as propan-2-ol or a glycol ether. Alternatively, pour-on, spot-on or spray formulations can be prepared by encapsulation, to leave a residue of active agent on the surface of the animal, this effect may ensure that the compound of the present invention has increased persistence of action and is more

durable, for example it may be more water-fast. Topical formulations contemplated herein can comprise from about 0.1 mg/kg to 50 mg/kg of a compound of the present invention, and more preferably from about 1 mg/kg to 10 mg/kg of a compound of the present invention, and even more preferably, from 1mg/kg to 5 mg/kg.

The compounds of the present invention can also be administered topically via a support matrix for example, a synthetic or natural resin, plastic, cloth, leather, or other such polymeric system in the shape of a collar or ear tag. Said collar or ear tag may be coated, impregnated, layered, by any means so as to provide a veterinary acceptable amount of a compound of the present invention alone, or with at least one veterinary acceptable excipient, and optionally an additional antiparasitic agent, or veterinary acceptable salts thereof. Such formulations are prepared in a conventional manner in accordance with standard medicinal or veterinary practice. Further, these formulations will vary with regard to the weight of active compound contained therein, depending on the species of host animal to be treated, the severity and type of infection or infestation, and the body weight of the animal. The volume of the applied composition can be from about 0.2 mL/kg to 5 mL/kg and preferably from about 1 mL/kg to 3mL/kg.

Agents may be added to the formulations of the present invention to improve the persistence of such formulations on the surface of the animal to which they are applied, for example to improve their persistence on the coat of the animal. It is particularly preferred to include such agents in a formulation which is to be applied as a pour-on or spot-on formulation. Examples of such agents include acrylic copolymers and in particular fluorinated acrylic copolymers. A particular suitable reagent is the trademark reagent “Foraperle” (Redline Products Inc, Texas, USA). Certain topical formulations may include unpalatable additives to minimize oral exposure.

The compounds of the present invention can also be administered by injection. Injectable (*e.g.*, subcutaneous and parenteral) formulations may be prepared in the form of a sterile solution, which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood. Acceptable liquid excipients include vegetable oils such as sesame oil, glycerides such as triacetin, esters such as benzyl benzoate, isopropyl myristate and fatty acid derivatives of propylene glycol, as well as organic solvents such as pyrrolidin-2-one and glycerol formal. The formulations are prepared by dissolving or suspending

compounds of the present invention alone or with at least one additional antiparasitic agent in the liquid excipient such that the final formulation contains from about 0.01 to 30% by weight of the active ingredients.

Suitable devices for injectable administration include needle (including micro needle) injectors, needle-free injectors and infusion techniques. Injectable formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dry powder form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of injectable formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard veterinary techniques well known to those skilled in the art. The solubility of a compound of the present invention used in the preparation of an injectable solution may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Administration of the compound of the instant invention is contemplated to be once a month. However, an extended duration formulation may allow for dosing once every 2, 3, 4, 5, or 6 months.

Such formulations are prepared in a conventional manner in accordance with standard medicinal or veterinary practice. Further, these formulations will vary with regard to the weight of active compound contained therein, depending on the species of host animal to be treated, the severity and type of infection or infestation, and the body weight of the animal.

The composition of the present invention may be administered alone, as described above, or in combination with at least one other additional antiparasitic agent to form a multi-component parasiticide giving an even broader spectrum of veterinary utility. Thus, the present invention also envisions a combination veterinary composition comprising an effective amount of the compound of the present invention in combination with at least one other additional antiparasitic agent and can further comprise at least one veterinary acceptable excipient.

The following list of additional antiparasitic agents together with which the compound of the present invention can be used is intended to illustrate the possible combinations, but not to impose any limitation. Non-limiting examples of additional antiparasitic agents include: amitraz, aminoacetonitriles, albendazole,

cambendazole, fenbendazole, flubendazole, thiabendazole, mebendazole, cyclic octadepsipeptides, oxfendazole, oxibendazole, paraherquamide, parbendazole, piperazines, praziquantel, thiabendazole, tetramisole, triclabendazole, levamisole, pyrantel (including the salt forms - pamoate, citrate, and tartrate), oxantel, morantel, abamectin, doramectin, emamectin, eprinomectin, ivermectin, moxidectin, selamectin, dimadectin, latidectin, lepimectin, milbemycin, milbemycin oxime, demiditraz, emodepside, fipronil, methoprene, diethylcarbamazine, hydroprene, kinoprene, lufenuron, metaflumizone, niclosamide, permethrin, pyrethrins, pyriproxyfen, closantel, clorsulon, novaluron, fluazuron, spinosad, sarolaner ((S)-1-(5'-(5-(3,5-dichloro-4-fluorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl)-3'H-spiro[azetidine-3,1'-isobenzofuran]-1-yl)-2-(methylsulfonyl)-ethan-1-one), fluralaner (4-(5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydro-isoxazol-3-yl)-2-methyl-N-(2-oxo-2-((2,2,2-trifluoroethyl)amino)-ethyl)benzamide), afoxolaner (4-(5-(3-chloro-5-(trifluoromethyl)phenyl)-5-(trifluoromethyl)-4,5-dihydro-isoxazol-3-yl)-N-(2-oxo-2-((2,2,2-trifluoroethyl)amino)ethyl)-1-naphthamide), lotilaner (3-methyl-N-{2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl}-5-[(5S)-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]thiophene-2-carboxamide); and mixtures thereof. Preferred additional antiparasitic agents include moxidectin, doramectin, selamectin, abamectin, milbemycin, milbemycin oxime, pyrantel, praziquatel, and levamisole.

The veterinary composition for application to an animal may be packaged in a variety of ways depending upon the method used for administering the compound of the present invention or combination, thereof. Generally, an article for distribution includes a container having deposited therein the veterinary composition in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

The compounds of the present invention (including the compositions and processes used therein) may also be used in the manufacture of a medicament for the therapeutic applications described herein.

The compounds of the present invention, stereoisomers thereof, and compositions comprising a therapeutically effective amount of a Formula (1)

compound and at least one veterinary acceptable excipient are useful as ectoparasiticides for the control and treatment of infections or infestations manifested by said ectoparasite in an animal. The compounds of the present invention have utility as an ectoparasiticide, in particular, as an acaricide and insecticide. They may, in particular, be used in the fields of veterinary medicine, livestock husbandry and the maintenance of public health: against acarids, insects, and copepods which are parasitic upon vertebrates, particularly warm-blooded vertebrates, including companion animals, livestock, and fowl and cold-blooded vertebrates like fish.

The compounds of the present invention are useful for the treatment of parasitic worms categorized as cestodes (tapeworms), nematodes (roundworms) and trematodes (flatworms or flukes). The gastrointestinal roundworms include, for example, *Ostertagia ostertagi (*including inhibited larvae*), O. lyrata, Haemonchus placei, H. similis, H. contortus, Toxocara canis, T.leonina, T. cati, Trichostrongylus axei, T. colubriformis, T. longispicularis, Cooperia oncophora, C. pectinata, C. punctata, C. surnabada (syn. mcmasteri), C. spatula, Ascaris suum, Hyostrongylus rubidus, Bunostomum phlebotomum, Capillaria bovis, B. trigonocephalum, Strongyloides papillosus, S. ransomi, Oesophagostomum radiatum, O. dentatum, O. columbianum, O. quadrispinulatum, Trichuris spp.,* and the like. Other parasites include: hookworms *(e.g., Ancylostoma caninum, A.tubaeforme, A.braziliense, Uncinaria stenocephala);* lungworms *(e.g., Dictyocaulus viviparus and Metastrongylus spp);* eyeworms *(e.g., Thelazia spp.);* parasitic stage grubs *(e.g., Hypoderma bovis, H. lineatum, Dermatobia hominis);* kidneyworms *(e.g., Stephanurus dentatus);* screw worm *(e.g., Cochliomyia hominivorax (larvae*); filarial nematodes of the super-family *Filarioidea* and the *Onchocercidae* Family. Non-limiting examples of filarial nematodes within the *Onchocercidae* Family include the genus *Brugia spp. (i.e., B.malayi, B. pahangi, B. timori,* and the like*), Wuchereria spp. (i.e., W. bancrofti, and the like), Dirofilaria spp. (D. immitis, D. repens, D. ursi, D. tenuis, D.spectans, D. lutrae,* and the like*), Dipetalonema spp. (i.e., D reconditum, D. repens, and the like), Onchocerca spp. (i.e., O. gibsoni, O. gutturosa, O. volvulus,* and the like*), Elaeophora spp. (E.bohmi, E. elaphi, E. poeli, E. sagitta, E. schneideri,* and the like*), Mansonella spp. (i.e., M. ozzardi, M. perstans,* and the like*), and Loa spp. (i.e., L. loa).* In another aspect of the invention, the compound of the present invention is useful for treating endoparasiticidal infection from filarial nematodes

within the genus *Dirofilaria (i.e., D .immitis, D. repens, D. ursi, D. tenuis,* and the like).

The compounds of the present invention can also be used against ectoparasites, alone or in combination with at least one additional antiparasitic agent. Some non-limiting examples of ectoparasites include: ticks (*e.g., Ixodes spp.,* (*e.g., I. ricinus, I. hexagonus*), *Rhipicephalus spp.,(e.g., R. sanguineus), Boophilus spp., Amblyomma spp. (e.g., A. maculatum, A. triste, A. parvum, A. cajennense, A. ovale, A. oblongoguttatum, A. aureolatum, A. cajennense), Hyalomma spp., Haemaphysalis spp., Dermacentor spp. (e.g., D. variabilis, D. andersoni, D. marginatus), Ornithodorus spp., and the like);* mites *(e.g., Dermanyssus spp., Sarcoptes spp.,(e.g., S. scabiei), Psoroptes spp., (e.g., P/ bovis), Otodectes spp., Chorioptes spp., Demodex spp., (e.g., D. folliculorum, D. canis, and D. brevis) and the like);* chewing and sucking lice *(e.g., Damalinia spp., Linognathus spp., Cheyletiella spp., Haematopinus spp., Solenoptes spp., Trichodectes spp., Felicola spp.,* and the like); fleas *(e.g., Siphonaptera spp., Ctenocephalides spp.,* and the like); biting flies, midges, and mosquitos *(e.g., Tabanidae spp., Haematobia spp., Musca spp., Stomoxys spp., Dematobia spp., Cochliomyia spp., Simuliidae spp., Ceratopogonidae spp., Psychodidae spp., Aedes spp., Culex spp., Anopheles spp.,* and the like); bed bugs *(e.g., insects within the genus Cimex and family Cimicidae);* and grubs *(e.g.,Hypoderma bovis, H.lineatum);* and copepods *(e.g.,* sea lice within the Order *Siphonostomatoida,* including genera *Lepeophtheirus and Caligus).*

The compounds of the present invention and compositions comprising compounds of the present invention in conjunction with at least one other antiparasitic agent are of particular value in the control of ectoparasites and endoparasites which are injurious to, or spread or act as vectors of diseases in companion animals, livestock, birds, and fish. The ectoparasites and endoparasites which can be treated with a combination of a Formula (1) compound and an additional antiparasitic agent include those as herein before described.

Any of the compounds of the present invention, or a suitable combination of a compound of the present invention and optionally, with at least one additional antiparasitic agent may be administered directly to the animal and/or indirectly by applying it to the local environment in which the animal dwells (such as bedding, enclosures, and the like). Direct administration includes contacting the skin, fur, or

feathers of a subject animal with the compound(s), or by feeding or injecting the compounds into the animal.

The Formula (1) compound, stereoisomers thereof, veterinary acceptable salts thereof, and combinations with at least one additional antiparasitic agent, as described herein, are of value for the treatment and control of the various lifecycle stages of parasites including egg, nymph, larvae, juvenile and adult stages.

The present invention also relates to a method of administering a compound of the present invention alone or in combination with at least one additional antiparasitic agent, and optionally at least one veterinary acceptable excipient, to animals in good health comprising the application to said animal to reduce or eliminate the potential for human parasitic infection or infestation from parasites carried by the animal and to improve the environment in which the animals inhabit.

The present invention also relates to a method of administering a compound of the present invention alone or in combination with at least one additional antiparasitic agent, and optionally at least one veterinary acceptable excipient, to a human in good or poor health comprising the application to said human to reduce or eliminate the potential for human parasitic infection or infestation from parasites carried by the human and to improve the environment in which the human inhabits.

The present invention also relates to a method of administering a compound of the present invention alone or in combination with at least one additional antiparasitic agent, and optionally at least one veterinary acceptable excipient, to a plant or soil to prevent parasitic infection to the plant.

The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks can be fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed using glass-backed silica gel 60 F 254 precoated plates and eluted with appropriate solvent ratios (v/v). Reactions were assayed by TLC or LCMS and terminated as judged by the consumption of starting material. Visualization of the TLC plates was done with UV light (254 nM wavelength) or with an appropriate TLC visualizing solvent and activated with heat. Flash column chromatography (Still et al., J. Org. Chem. 43, 2923, (1978) was performed using silica gel (RediSep Rf) or various MPLC systems, such as Biotage or ISCO purification system.

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well-known to one of ordinary skill in the art and may include, for example, all types of chromatography (*e.g.*, high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography (TLC), recrystallization, and differential (*i.e.*, liquid-liquid) extraction techniques.

The compound structures in the examples below were confirmed by one or more of the following methods: proton magnetic resonance spectroscopy, and mass spectroscopy. Proton magnetic resonance (1H NMR) spectra were determined using a Bruker spectrometer operating at a field strength of 400 megahertz (MHz). Chemical shifts are reported in parts per million (ppm) downfield from an internal tetramethylsilane standard. Mass spectra (MS) data were obtained using Agilent mass spectrometer with atmospheric pressure chemical ionization. Method: Acquity UPLC with chromatography performed on a Waters BEH C18 column (2.1 x 50 mm, 1.7 μm) at 50°C. The mobile phase was a binary gradient of acetonitrile (containing 0.1% trifluoroacetic acid) and water (5-100%).

Certain aspects of the present invention are illustrated by the following Examples. It is to be understood, however, that the aspects of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

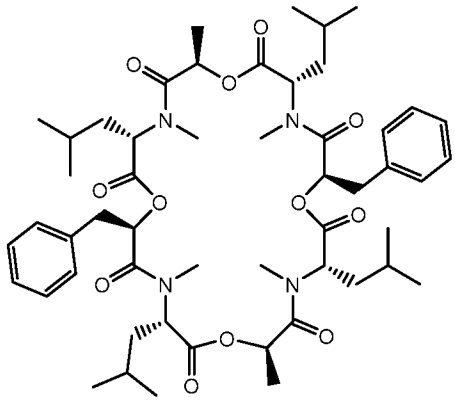
Compounds of this invention can exist as one or more stereoisomers. One skilled in the art will appreciate that one stereoisomer may be more active and/or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich, and/or to selectively prepare said stereoisomers. The compounds of the invention may be present as a mixture of stereoisomers.

In the Schemes and Examples described below, the following catalysts/reactants and miscellaneous abbreviations include: room temperature (RT, or rt); dichloromethane (DCM); methanol (MeOH), ethanol (EtOH); tetrahydrofuran (THF); 4-dimethylaminopyridine (DMAP); t-butyloxycarbonyl (BOC, boc); palladium (Pd); palladium on carbon (Pd/C); N,N-diisopropylethylamine (DIPEA); 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI); methoxymethyl chloride (MOM-Cl);

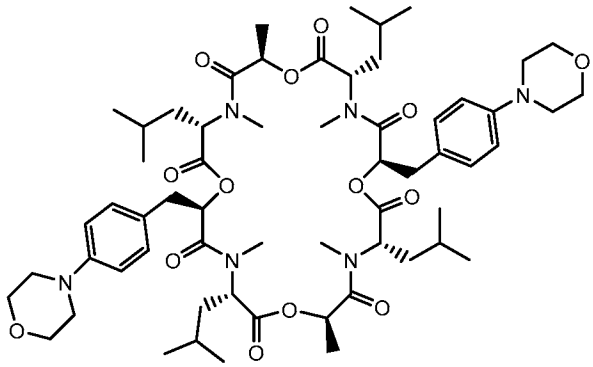
methoxy methyl bromide (MOM-Br); protecting group (Pg); saturated aqueous (Sat Aq); dimethyl formamide, sulfuric acid (H_2SO_4); iron (Fe); ethyl acetate (EtOAc); water (H_2O); ammonium chloride (NH_4Cl); triethylamine (TEA; NEt_3); dimethyl formamide (DMF); dimethylsulfoxide (DMSO); hydrochloric acid (HCl); sodium hydroxide (NaOH); acetonitrile (CH_3CN); hydrogen peroxide (H_2O_2); trifluoroacetic acid TFA); benzyl bromide (BnBr); cesium carbonate (Cs_2CO_3); methyl iodide (MeI); sodium hydride (NaH); sodium nitrite ($NaNO_2$); sodium carbonate (Na_2CO_3); magnesium sulfate ($MgSO_4$); denatured alcohol (IMS); 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC); N-methyl morpholine (NMM); hydrogen (H_2-gas); triphenylphosphine (PPh_3); Tri-Cl (trityl chloride); di-tert-butyl-azodicarboxylate (DBAD); propylphosphonic anhydride (T_3P); hydrogen bromide (HBr); acetic acid (AcOH); copper iodide (CuI); sodium borohydride ($NaBH_4$); thionyl chloride ($SOCl_2$); potassium carbonate (K_2CO_3); acetic anhydride (Ac_2O); lithium aluminum hydride (LiAlH); sodium ethoxide (NaOEt); nitric acid (HNO_3); sodium sulfate (Na_2SO_4); dimethoxy ethane (DME); tetrahydropyran (THP); zinc dicyanide ($Zn(CN)_2$); aluminum chloride ($AlCl_3$); para-toluenesulfonic acid (PTSA); 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU); [1,1′-Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$); zinc chloride ($ZnCl_2$); potassium bicarbonate ($KHCO_3$); sodium bicarbonate ($NaHCO_3$); isopropyl magnesium chloride.lithium chloride (iPrMgCl-LiCl); diethyl azodicarboxylate (DEAD); thiamine pyrophosphate (TPP); pyridine (Py); lithium tert-butoxide (t-BuOli); di-tertbutyl decarbonate ($(Boc)_2O$); 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6); palladium hydroxide on carbon ($H_2Pd(OH)_2$); octyl 3-chloropropanoate ($HIS(octyl)_3$); tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$; Pd(TPP)4); and bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$).

EXAMPLES

PF1022A: (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-dibenzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone



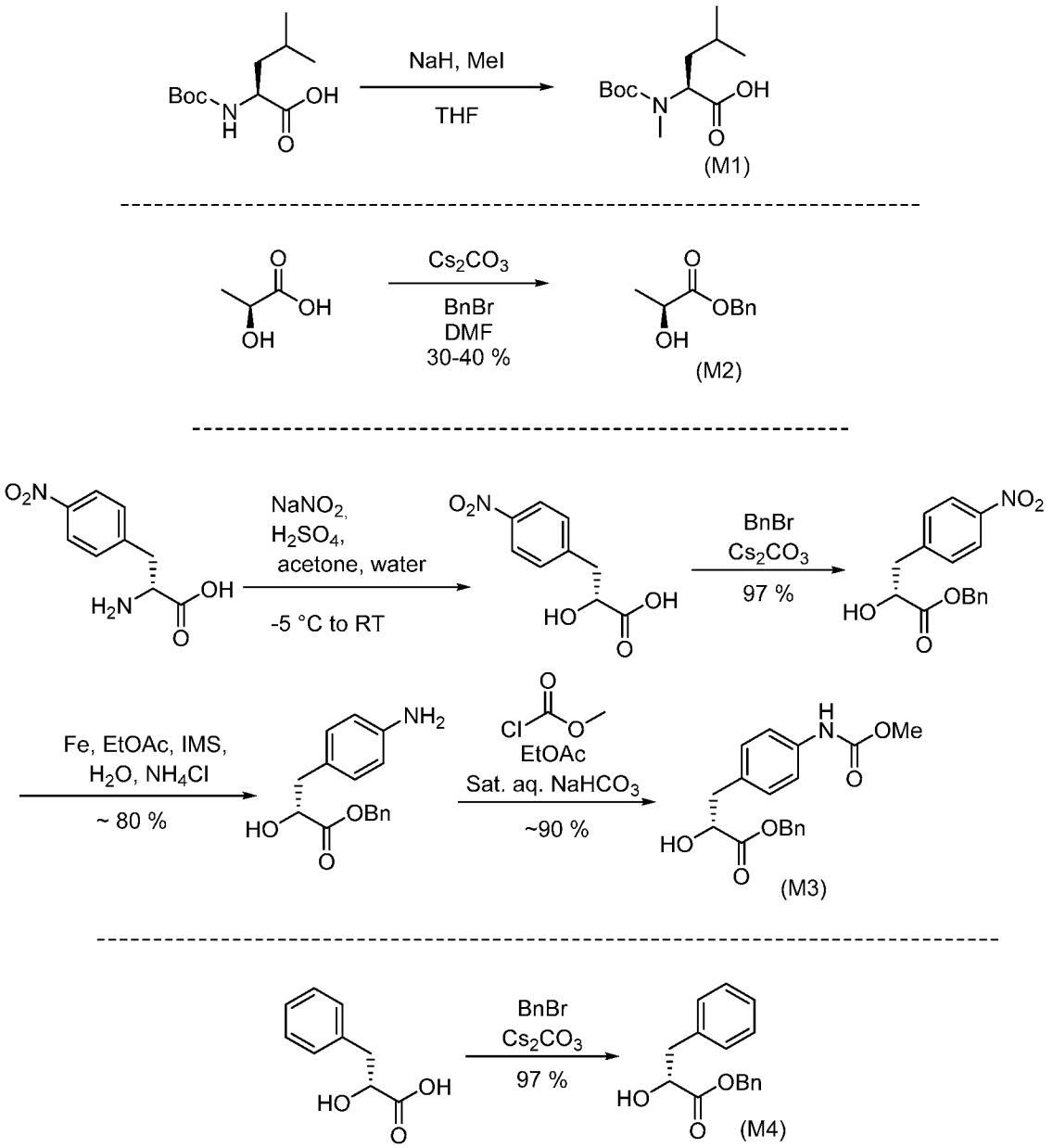
Emodepside: (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-morpholinobenzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone



The following examples were prepared according to the Schemes and preparations as presented herein.

(Intermediate schemes 1a-1r) – Preparation of Monomers

Scheme 1a: Synthetic Scheme for Preparation of Monomers M1, M2, M3 and M4.



In Scheme 1a, synthesis of monomers M1, M2, M3 and M4 was carried out by procedures well known in the literature. (Journal of Organic Chemistry, 79(17), 8491-8497; 2014; Organic Letters, 15(24), 6132-6135; 2013; ChemBioChem, 9(8), 1235-1242; 2008) These monomers were used in a stepwise synthesis of the PF1022a core as shown in subsequent schemes. In addition, the allyl protected monomers, allyl (S)-2-hydroxypropanoate and allyl (R)-2-hydroxy-3-(4-nitrophenyl)propanoate and allyl (R)-2-hydroxy-3-phenylpropanoate were also prepared according to the following literature procedures: Faming Zhuanli Shenqing,

101962323, 02Feb2011 and Journal of Organic Chemistry, 67(4), 1061-1070; 2002). These allyl protected monomers were used in an alternative route which also provided Bis-Iodo PF1022a using the same coupling conditions described below and the requisite chemistry to remove the allyl protecting group as described in T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Synthesis of Boc-Methyl-L-Leucine (M1):

Sodium hydride (65.16g, 1.63mol) was added portion-wise over 1.25 hours to a mixture of Boc-L-leucine(125g, 0.50mol) and iodomethane (160mL, 2.50mol) in THF (2L) cooled to 0°C. The temperature was maintained below 5°C during the addition and then allowed to warm up to room temperature and stirred for 2.5 days. The reaction mixture was cooled to 0°C and quenched with water (2L); the temperature was maintained below 5°C during the addition and then allowed to warm up to room temperature. The aqueous layer was extracted with EtOAc (2 × 750mL), then the aqueous was acidified to pH 5 with 10% aqueous citric acid solution, extracted with EtOAc (3×1L), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* (50°C) and azeotroped with DCM. The two batches were combined to yield 236.09 g, 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.85 (t, 0.5H), 4.61 (dd, 0.5H), 2.81 (s, 1.5H), 2.78 (s, 1.5H), 1.77-1.65 (m, 2H), 1.57-1.51 (m, 1H), 1.45 (s, 9H), 0.95-0.92 (m, 6H). Chiral analysis: 99.5% e.e. by GC.

Synthesis of Benzyl-L-Lactate (M2):

L-Lactic acid (467g, 5.2mol, anhydrous) was dissolved in DMF (1L). Cesium carbonate (847g, 2.6mol, 0.5eq) was added with stirring, followed by benzyl bromide (886g, 5.18mol, 0.99eq) over about 45 minutes. The mixture was stirred at room temperature for 4 days, after which time analysis showed the reaction to be complete. Heteroneous mixture was filtered through Celite®; the filter cake was washed with ethyl acetate (2 x 500mL). The filtrate was extracted with water (2 x 500mL), saturated aqueous Na_2CO_3 (4 x 500mL) and brine (2 x 500mL), then concentrated *in vacuo* to yield a thick orange oil, 775g, 80%. This was purified by dry flash chromatography using EtOAc/heptane (0% to 10%) as eluent. Appropriate fractions were combined and concentrated *in vacuo* to yield benzyl-L-lactate, 385g, 41%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40-7.35 (m, 5H), 5.21 (s, 2 H), 4.37-4.27 (m, 1H), 2.79 (d, 1H), 1.43 (d, 3H).

Synthesis of benzyl (R)-2-hydroxy-3-(4-((methoxycarbonyl)amino)phenyl)propanoate (M3):

Step 1:

$NaNO_2$ (147.6g, 2.13mol) in water (600mL) was added drop-wise to a mixture of 4-nitro-D-phenylalanine, (150g, 0.71mol) in 1M H_2SO_4 (aqueous, 900 mL), water (750mL) and acetone (2.25L) maintaining a temperature between -5°C and -3°C. The mixture was stirred at -5°C for 1.5 hours then allowed to warm to room temperature and stirred for 3 days. The mixture was concentrated *in vacuo* to remove the acetone and the mixture was extracted with EtOAc (5×~375mL), the combined organics were dried over $MgSO_4$ filtered and the solvent removed *in vacuo* to yield a yellow solid that was recrystallised from isopropyl acetate (~2.5 volumes), to yield p-nitrophenyl-D-lactic acid (68.38g, 45%) as a yellow solid; a second crop 6.25g (combined yield 50%) was obtained from the residue by slurrying in DCM. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (d, 2H), 7.45 (d, 2H), 4.59-4.54 (m, 1H), 3.31 (dd, 1H), 3.10 (dd, 1H). No chiral analysis was performed.

Step 2:

Cs_2CO_3 (123.3g, 378mmol) was added to a mixture of p-nitophenyl-d-lactic acid (156.75g, 742mmol) in DMF (700mL) and stirred for 15 minutes, gas was evolved and the heterogenous solution cleared yielding a homogenous brown solution (a mild exotherm was observed). Benzyl bromide (124.39g, 727mmol) in DMF (140mL) was added at room temperature over about 5 minutes; a precipitate formed and the mixture was stirred for about 20 hours at room temperature. The mixture was filtered through Celite® and the filter cake was washed with EtOAc (2×500mL), the filtrate was washed with water (2×500mL), saturated aqueous $NaHCO_3$ (3×500mL), and then brine (500mL). Heptane (about 1L) was added to the organic layer and the resultant off white precipitate was filtered off, further crops were obtained from the mother liquors after concentration and trituration with heptanes. The batches were dried at 40°C for about 18 hours and combined to yield an off white solid (197.6g, 88% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (m, 2H), 7.45-7.25 (m, 7H), 5.20 (dd, 2H), 4.55-4.48 (m, 1H), 3.25-3.00 (dd, 2H), 2.86 (d, 1H). UPLC (CSH_C18, Short acid 2-95%): 0.73 minutes; no mass ion observed.

Step 3:

Iron powder (256g, 4.59mol) was added to a stirred mixture of (R)-benzyl 2-hydroxy-3-(4-nitrophenyl)propanoate (197.5g, 0.66mol), ammonium chloride (455g,

8.52mol), EtOAc (1L), water (900mL), IMS (100mL) heated at 60ºC. The reaction became darker in colour and was stirred for 18 hours at 50°C. The mixture was cooled, filtered through Celite® and the filter cake was washed with EtOAc (about 600mL). The layers were separated, and the organic layer was washed with water (3×500mL). The organic layer was extracted with aqueous 1 M HCl (4×250mL); then the acidic extracts were basified with saturated aqueous $NaHCO_3$ until about pH 8-9. This was extracted into EtOAc (1L, then 2×500mL); the combined organic layers were concentrated *in vacuo* to yield a solid which was azeotroped with toluene, EtOAc, then DCM. The residue was dried at 50°C to yield an off white solid (146.5g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42-7.30 (m, 5H), 6.91 (d, 2H), 6.56 (d, 2H), 5.13 (s, 2H), 4.42 (t, 1H), 3.54 (s, br 1H), 3.08-2.80 (m, 2H). UPLC (CSH_C18, Short acid 2-95%): 0.32 min, 271.43 Da $[M+H]^+$.

Step 4:

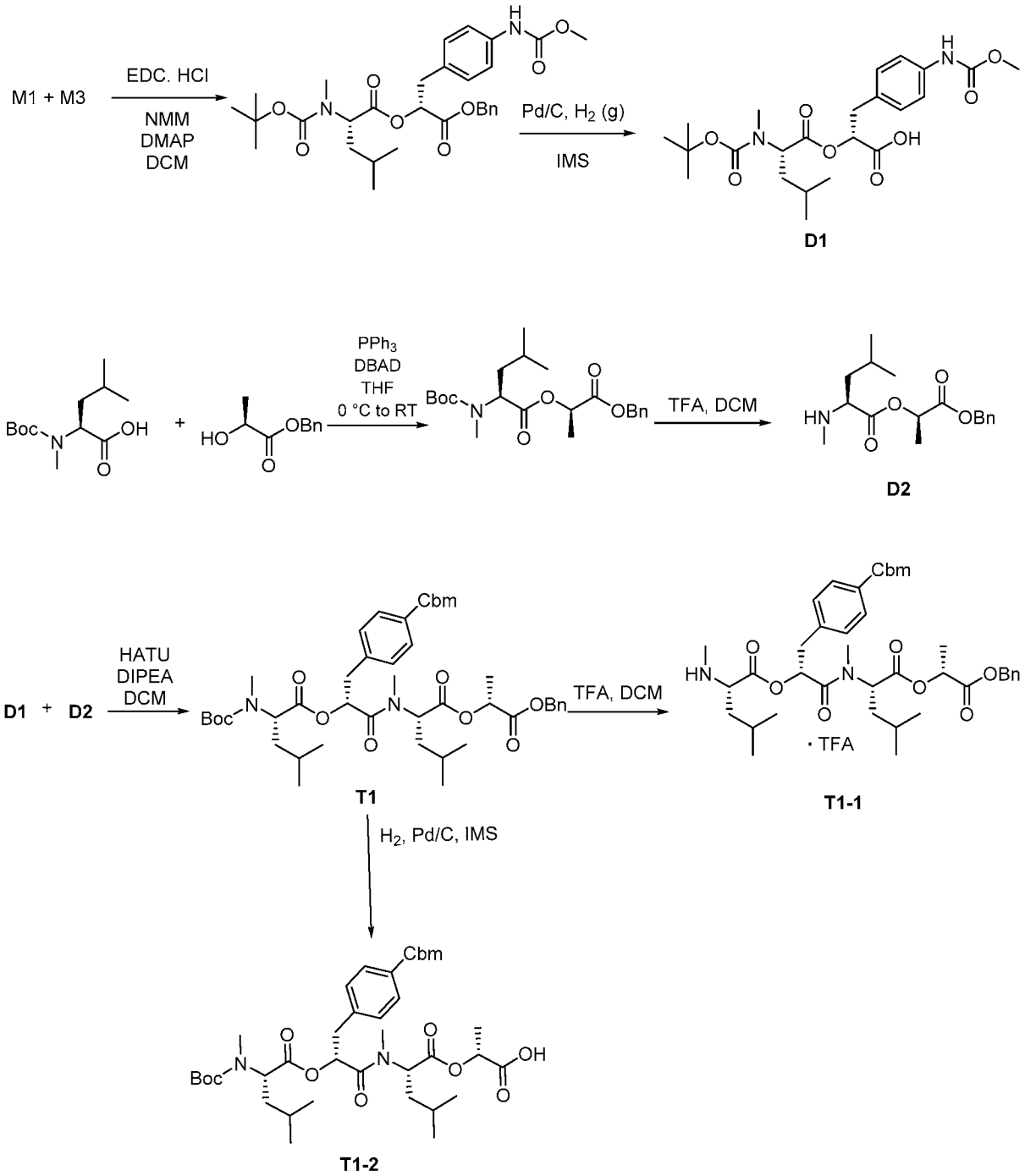
Methyl chloroformate (24.5mL, 316mmol, 1.5eq.), was added drop-wise to a stirred mixture of (R)-benzyl 3-(4-aminophenyl)-2-hydroxypropanoate (57.30g, 211mmol), EtOAc (375mL) and saturated aqueous $NaHCO_3$ (300mL, 5.2vol) at room temperature over about 20 minutes (a mild exotherm to about 25ºC was observed along with gas evolution). The mixture was stirred for a further 10 minutes, the organic layer was removed and washed with brine (200mL), dried over Na_2SO_4 filtered and concentrated *in vacuo* to yield M3 as a white solid (73.48g, 99% yield) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42-7.31 (m, 5H), 7.26-7.13 (m, 2H), 7.12-7.01 (m, 2H), 6.70 (s, 1H), 5.13-5.22 (m, 2H), 4.49-4.43 (m, 1H), 3.74 (s, 3H), 3.06 (dd, 1H), 2.93 (dd, 1H), 2.82 (d, 1H). UPLC (CSH_C18, Short acid 2-95%): 0.64 min, 330.4 Da $[M+H]^+$.

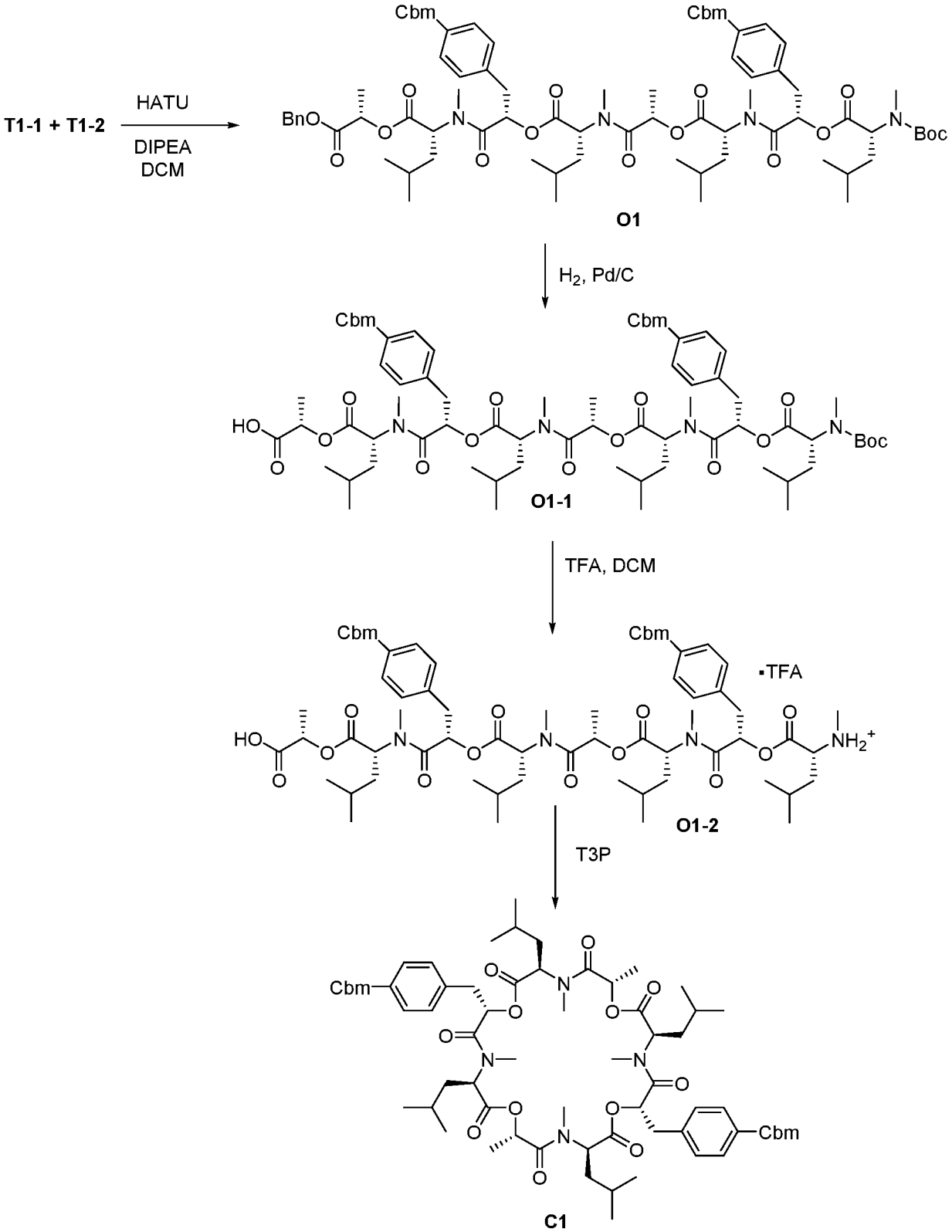
Synthesis of benzyl (R)-2-hydroxy-3-phenylpropanoate (M4)

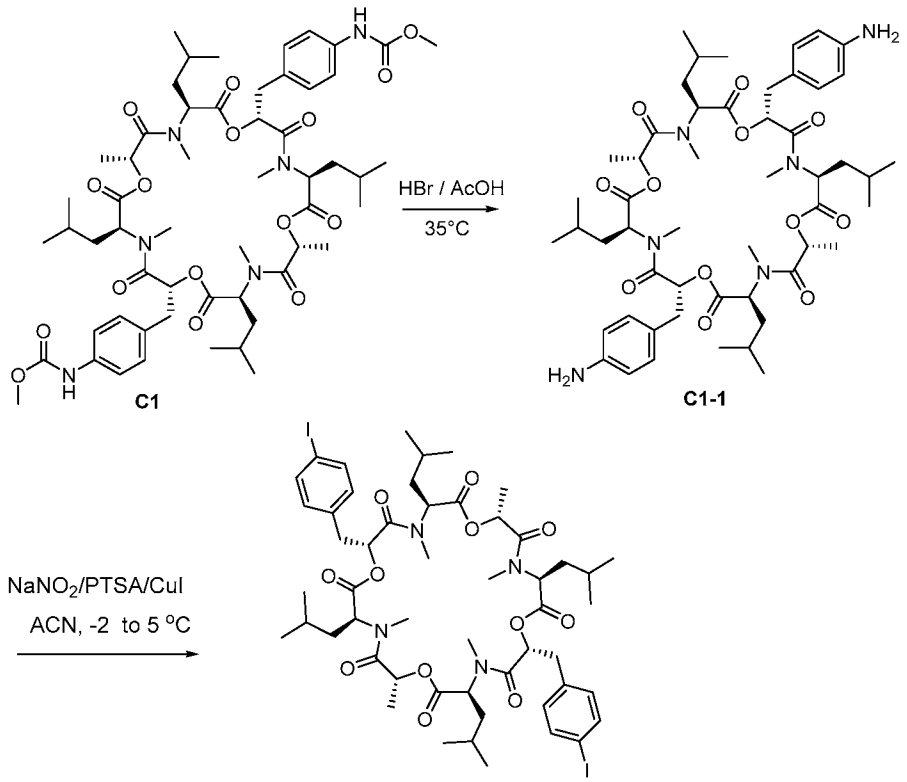
Cs_2CO_3 (97.5, 300 mmol) was added to a mixture of (R)-2-hydroxy-3-phenylpropanoic acid (100g, 602 mmol) in DMF (700mL) and stirred for 15 minutes, gas was evolved and the heterogenous solution cleared yielding a homogenous brown solution (a mild exotherm was observed). Benzyl bromide (102.0 g, 602mmol) in DMF (100mL) was added at room temperature over about 5 minutes; a precipitate formed and the mixture was stirred for about 20 hours at room temperature. The mixture was filtered through Celite® and the filter cake was washed with EtOAc (2×400mL), the filtrate was washed with water (2×400mL), saturated aqueous

$NaHCO_3$ (3×400mL), and then brine (300mL). Heptane (about 1L) was added to the organic layer and the resultant off white precipitate was filtered off, further crops were obtained from the mother liquors after concentration and trituration with heptanes. The batches were dried at 40°C for about 18 hours and combined to yield an off white solid (M4, 151 g, 89% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (m, 2H), 7.45-7.25 (m, 7H), 5.20 (dd, 2H), 4.55-4.48 (m, 1H), 3.25-3.00 (dd, 2H), 2.86 (d, 1H).

Scheme 1b. Route for Stepwise Synthesis of Bis-Iodo PF1022a




T1-1 + T1-2
HATU
DIPEA
DCM
Cbm
BnO
Boc
O1
H2, Pd/C
HO
O1-1
TFA, DCM
▪TFA
NH2+
O1-2
T3P
C1



As shown in Scheme 1b, dimers D1 and D2 are prepared using standard amide bond forming methods and ester bond forming methods followed by standard protecting group removal steps. Tetramer T1, is formed from the reaction of D1 with D2 using routine amide bond forming methods. T1 is then selectively deprotected to provide either of two tetramers, T1-1 and T1-2, which when coupled together provide the corresponding linear octadepsipeptide, O1. Sequential deprotection and cyclization yielded the appropriately aryl functionalized cyclic octadepsipeptide, C1. Conversion to the advanced intermediate Bis-Iodo PF1022a was accomplished by performing a two-step sequence that included protecting group removal followed by routine sequence to convert the amino group to an iodo group. It will be appreciated by ones skilled in the art that mono-Iodo PF1022a may be readily obtained from the route shown in Scheme 1b through the appropriate use of M3 and M4.

Synthesis of (R)-1-(benzyloxy)-3-(4-((methoxycarbonyl)amino)phenyl)-1-oxopropan-2-yl N-(tert-butoxycarbonyl)-N-methyl-L-leucinate (D1):

Step 1:

EDC.HCl (134.8g, 703mmol), was added in one portion to a mixture of (R)-benzyl 2-hydroxy-3-(4-((methoxycarbonyl)amino)phenyl)propanoate (178.2g, 541mmol), Boc-Methyl-L-Leucine (146.0g, 595mmol), DMAP (6.60g, 54mmol), 4-methylmorpholine (154.6mL, 406mmol) and DCM (3.4L). EDC.HCl slowly dissolves forming an orange solution; a mild exotherm was controlled by cooling after about15 minutes. After 5 hours the reaction was washed with water (2×2 L), 10% aqueous citric acid solution (2×1L), 5% aqueous citric acid solution (1×1L), saturated aqueous $NaHCO_3$, water (1L), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield an oil 296.1g, 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-6.95 (m, 9H), 6.67-6.45 (m, 1H), 5.36-4.64 (m, 4H), 4.14-3.63 (m, 3H), 3.22-2.92 (m, 2H), 2.74-2.50 (m, 3H), 1.69-1.32 (m, 12H), 1.01-0.79 (m, 6H). UPLC (CSH_C18, Short acid, 2-95%): 1.06 min, 457.6 Da, $[M-Boc+H]^+$.

Step 2:

Pd-C 10% w/w (20.7g, 19mmol) was washed into a solution of (R)-1-(benzyloxy)-3-(4-((methoxycarbonyl)amino)phenyl)-1-oxopropan-2-yl N-(tert-butoxycarbonyl)-N-methyl-L-leucinate (296g, 532mmol) in industrial methylated spirits (IMS, 3L) with toluene (about 80mL). The mixture was left to stir for about 18 hours under hydrogen (1 atm) for 2 days. The mixture filtered through Celite®, the filter cake was washed with IMS (about 500mL) and the mixture concentrated *in vacuo.* The residue was purified by filtering through a plug of silica eluting with 40% EtOAc in heptanes and concentrated *in vacuo* to yield D1. (232.72g, 91%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.25 (m, 2H), 7.17-7.11 (m, 2H), 6.94 (s, br 1H), 5.27-5.18 (m, 1H), 4.73-4.67 (m, 1H), 3.76 (s, 3H), 3.20-3.05 (m, 2H), 2.80-2.70 (m, 3H), 1.76-1.40 (m, 11H), 0.95-0.85 (M, 6H), 96.72% pure w/w by HNMR with 0.34% DCM and 1.60% EtOAc, equivalent to 225.08g, 90.6%. UPLC (CSH_C18, Short acid 2-95%): 0.86 min, 367.6 Da $[M-Boc+H]^+$.

Synthesis of Synthesis of (R)-1-(benzyloxy)-1-oxopropan-2-yl N-(tert-butoxycarbonyl)-N-methyl-L-leucinate (D2):

Step 1:

Triphenylphosphine (192g, 732mmol), Boc-Methyl-L-Leucine (165g, 672.6mmol), and benzyl-L-Lactate (120g, 666mmol) were dissolved in tetrahydrofuran (700mL). The resulting solution was cooled to 0°C, then di-tertbutylazodicarboxylate (192g, 834mmol, 1.25eq.) was added portionwise,

maintaining internal temperature < 5°C. Once addition complete, mixture was allowed to stir and warm to room temperature overnight, during which time an off-white precipitate had formed. Heptane (500mL) was added, and the resulting mixture filtered through Celite®. The cake was washed with heptane (2x100mL). The filtrate was concentrated *in vacuo* to yield a thick orange oil (602g). Heptane (500mL) was added, and the mixture was stirred vigorously for about 1 hour, resulting in further white precipitate forming. This was removed by filtration; the cake was washed with heptane (2x300mL). The resulting filtrate was loaded directly onto silica (2kg), and eluted with EtOAc/hetane (1% to 10%). First fraction (72.6g) still contained triphenylphosphine oxide; this was recolumned (about 700g silica, about 10% loading), using EtOAc/heptane (0% to 6%), to yield 68.2g (25.1%) of Boc-MeLeu-DLac-OBn. The second fraction from the initial column was concentrated *in vacuo* to yield 100.1g (combined = 168.3g, 62%) of (R)-1-(benzyloxy)-1-oxopropan-2-yl N-(tert-butoxycarbonyl)-N-methyl-L-leucinate as a straw coloured oil. ^{1}H NMR ($CDCl_3$): δ 7.46-7.30 (m, 5H), 5.21-5.08 (m, 3H), 4.99-4.70 (ddd, 1H), 2.73 (d, 3H), 1.73-1.40 (m, 18H), 0.92 (t, 6H). UPLC (CSH_C18, Short acid 2-95%): 1.08 min, 308.5 Da $[M-Boc+H]^+$.

Step 2:

(R)-1-(benzyloxy)-1-oxopropan-2-yl N-(tert-butoxycarbonyl)-N-methyl-L-leucinate (100.1g, 243mmol) was dissolved in dichloromethane (575mL, 5.75vol), and subsequently cooled to 0°C. Trifluoroacetic acid (150mL, 1.96mol, 8eq., 1.5vol) was then introduced. UPLC data after 4 hours indicated that reaction was about 50% complete. Further portion of trifluoroacetic acid (75mL, 980mmol, 4eq., 0.75vol) was added. UPLC indicated not complete after 7 hours, so mixture was stirred overnight for about 16 hours. Toluene (300mL) was added, and the mixture concentrated *in vacuo* to yield a thick orange oil, (D2) ^{1}H NMR shows residual toluene and trifluoroacetic acid. ^{1}H NMR ($CDCl_3$, 300 Mhz): 9.67-9.15 (br s, 1H), 8.65-8.10 (br s, 1H), 7.47-7.26 (m, 5H), 5.29-5.09 (m, 3H), 3.97-3.85 (m, 1H), 1.92-1.78 (m, 1H), 1.77-1.66 (m, 2H), 1.59-1.54 (s, 3H), 0.98-0.90 (m, 6H).
UPLC (CSH_C18, Short acid 2-95%): 0.43 min, 308.5 Da $[M+H]^+$.

Synthesis of (R)-1-(benzyloxy)-1-oxopropan-2-yl N-((R)-2-((N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)oxy)-3-(4-((methoxycarbonyl)amino)phenyl)propanoyl)-N-methyl-L-leucinate (T1):

D1 (193g, 458mmol) and D2 (225g, 482mmol) were stirred in dichloromethane (2L). HATU (250g, 658mmol, 1.36eq.) was added, followed by diisopropylethylamine (375mL, 2150mmol) through a dropping funnel. Temperature of reaction was maintained with the use of an external ice-bath. The mixture was allowed to stir overnight at room temperature. The reaction mixture was washed with water (3x2L), aqueous citric acid (10%, 2x1L), saturated aqueous $NaHCO_3$ (2x1L), and water (1L). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield an orange oil. This was purified by dry flash chromatography using EtOAc/heptane as eluent (0% to 30%), to yield T1 (313 g, 83 %).
^{1}H NMR ($CDCl_3$,300 MHz): δ 7.41-7.26 (m, 7H), 7.20-7.10 (m, 2H), 6.59 (s, 1H), 5.42-4.60 (m, 6H), 3.82-3.71 (m, 3H), 3.10-2.96 (m, 2H), 2.93-2.71 (m, 6H), 1.77-1.36 (m, 18H), 1.01-0.83 (m, 12H). UPLC (CSH_C18, Short acid, 2-95%): 1.14 min, 656.9 Da $[M-Boc+H]^+$.

Synthesis of (R)-1-(benzyloxy)-1-oxopropan-2-yl N-((R)-3-(4-((methoxycarbonyl)amino)phenyl)-2-((methyl-L-leucyl)oxy)propanoyl)-N-methyl-L-leucinate (T1-1):

T1 (48.7g, 64.4mmol) was dissolved in dichloromethane (300mL, 6vol). The resulting solution was cooled to 0°C with an external ice-bath. Trifluoroacetic acid (75mL, 980mmol, 1.5vol) was added to the reaction mixture and the mixture stirred until complete. Toluene (300mL) was added, and the mixture concentrated *in vacuo* yield a thick orange oil, 65.3g, about 125 % (cont ~ 16g of trifluoroacetic acid). Used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40-7.23 (m, 9H), 6.73 (s, 1H), 5.50-5.42 (m. 1H), 5.29-5.08 (m, 4H), 3.87-3.83 (m, 1H), 3.79-3.77 (m, 3H), 3.06 (d, 2H), 3.01-2.90 (m, 3H), 2.70-2.64 (m, 3H), 2.36 (m, 3H), 1.76-1.42 (m, 6H), 1.39-1.25 (m, 2H), 1.04-0.96 (m, 1H), 0.94-0.87 (m, 6H), 0.79-0.76 (m, 6H). UPLC (CSH_C18, Short acid 2-95%): 0.65 min, 656.91 Da $[M+H]^+$.

Synthesis of (6S,9R,12S,15R)-6,12-diisobutyl-9-(4-((methoxycarbonyl)amino)-benzyl)-2,2,5,11,15-pentamethyl-4,7,10,13-tetraoxo-3,8,14-trioxa-5,11-diazahexadecan-16-oic acid (T1-2):

Pd-C (10% w/w, 2.5g, 2.3mmol) was washed into a solution of T1 (48.3g, 63.9mmol) in IMS (500 mL) with toluene (about 20mL) and stirred under hydrogen (1atm) for 4 hours, filtered and the solvent removed *in vacuo* and then azeotroped

with DCM to yield Boc-MeLeu-DCbmPheLac-MeLeu-DLac-OH as an off-white foam 48.87g, 115% yield (used crude in subsequent reaction). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.05-7.29 (m, 4H), 5.70 (t, 1H), 4.65-5.45 (m, 5H), 3.75 (d, 3H), 2.68-3.19 (m, 8H), 2.30-2.34 (m, 1H), 1.38-1.74 (m, 17H), 1.10-1.29 (m, 1H), 0.83-0.99 (m, 13H). UPLC (CSH_C18, Short acid 2-95%): 0.97 min, 610.8 Da $[M-^tBu+H]^+$, 664.8 Da $[M-H]^-$.

Syntheisis of dimethyl ((((2S,5R,8S,11R,14S,17R,20S,23R)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))dicarbamate (C1):

Step 1:

T1-1 (49.3g, actual mass 65.3g, contains ~ 16 g trifluoroacetic acid, 64.4mmol) and T1-2 (42.5g, actual mass 48.5g, contains residual solvent from hydrogenation) were dissolved in dichloromethane (500mL). The mixture was cooled with an external ice-bath. HATU (36.4g, 95.7mmol, 1.5eq.) was added, followed by diisopropylethylamine (70mL, 400mmol, 6.3eq.). The resulting mixture was stirred for 20 hours. Water (1L) was added to the reaction mixture, and vigorously stirred for 0.83 hours. The layers were separated, and the organic phase washed with aq. citric acid (10%, 3x700mL), saturated aqueous $NaHCO_3$ (1x700 mL), and brine (1x500mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo* directly onto Celite® (150g) and silica gel (20g). The material was dry loaded onto a column of silica (1kg) and purified by dry flash chromatography using EtOAc/heptane (0-50%) as eluent. This afforded, after concentration *in vacuo,* O1 , 85 g, 101 % (some trace heptane observable in ^{1}H NMR spectrum). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06-7.34 (m, 13H), 6.61 (s, 1H), 4.58-5.46 (m, 10H), 3.73-3.76 (m, 6H), 2.66-3.16 (m, 15H), 1.16-1.69 (m, 28H), 0.83-0.98 (m, 24H). UPLC (CSH_C18, Long acid, 2-95%): RT 3.53 min, 1204.5 Da, $[M-Boc+H]^+$.

Step 2:

O1 (199.5 g, 153 mmol) was dissolved in IMS (400 mL, 2 vol) and charged to the 2 L autoclave. 5% Pd/C (2 g) was added as a paste in toluene. The autoclave was sealed and charged to 150 psi hydrogen pressure. After stirring for 5 h at RT, 16% starting material remained so the autoclave was recharged to 150 psi and allowed to stir at RT overnight. The reaction was complete by UPLC, so the

autoclave was vented and the catalyst removed by filtration through Whatman GF/A media, washing with IMS (50 mL) and ethyl acetate (200 mL). The solvent was removed on the rotary to leave a white foam, O1-1 (175 g, 94% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.06-7.34 (m, 8H), 4.58-5.46 (m, 10H), 3.73-3.76 (m, 6H), 2.66-3.16 (m, 15H), 1.16-1.69 (m, 28H), 0.83-0.98 (m, 24H). UPLC (Long acid, 2-95%): RT 3.36 min, 1113.5 Da, $[M-Boc+H]^+$.

Step 3:

O1-1 (245 g, 202 mmol) was dissolved in DCM (1.5 L, 6 vol) and cooled to <10°C (ice/water bath). Trifluoroacetic acid (370 mL, 551 g, 1.5 vol) was added and the solution allowed to warm to RT and stirred overnight. The solvent was removed on the rotary and azeotroped with toluene (2 x 500 mL). The product was obtained as a thick orange oil O1-2 (359.5 g, overweight – estimated purity from NMR is 65%, giving calculated mass of 234 g, 94% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.91 (s, TFA), 7.1-7.35 (m, 8H), 4.6-5.65 (m, 8H), 3.79 (s, 6H), 2.6-3.2 (m, 18H), 1.1-1.9 (m, 16H), 0.65-1.07 (m, 28H).

Step 4:

A solution of O1-2 (359.5g, 65% purity, 0.190mol) in DCM (2.5L) was added slowly over 1.5 hours to a solution of propylphosphonic anhydride (50% solution in EtOAc, 670mL, 1.126mol) and diisopropylethylamine (392mL, 2.25mol) in DCM (2.5L), maintaining the temperature between 20 and 22°C. When the addition was complete, the solution was allowed to stir for a further 20 minutes and the reaction was checked for completion by UPLC. The solvent was removed on the rotary and replaced with EtOAc (5L). The solution was washed with potassium hydrogen sulphate solution (1M, 2x1L), 3% sodium carbonate solution (2x1.5L) and brine (1L). The organic layer was dried over $MgSO_4$ and filtered through Fisherbrand QL100 paper twice. The solvent was removed to leave a yellow foam (233g). This was recrystallised from ethanol (660mL) and water (130mL) and the product was washed with ethanol/water (600mL, 3:1). The product was dried on the filter bed and further dried on the rotary at 60°C. The product, C1, was obtained as a white solid (159.2g, 77% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.3 (m, 4H), 7.15 (m, 4H), 4.4-5.67 (m, 8H), 3.76 (s, 6H), 2.7-3.1 (m, 16H), 1.16-1.8 (m, 16H), 0.73-1.1 (m, 28H). UPLC (Short acid 2-95%): 1.08 min, 1095.5 Da $[M+H]^+$.

Synthesis of Bis-Iodo PF1022a:

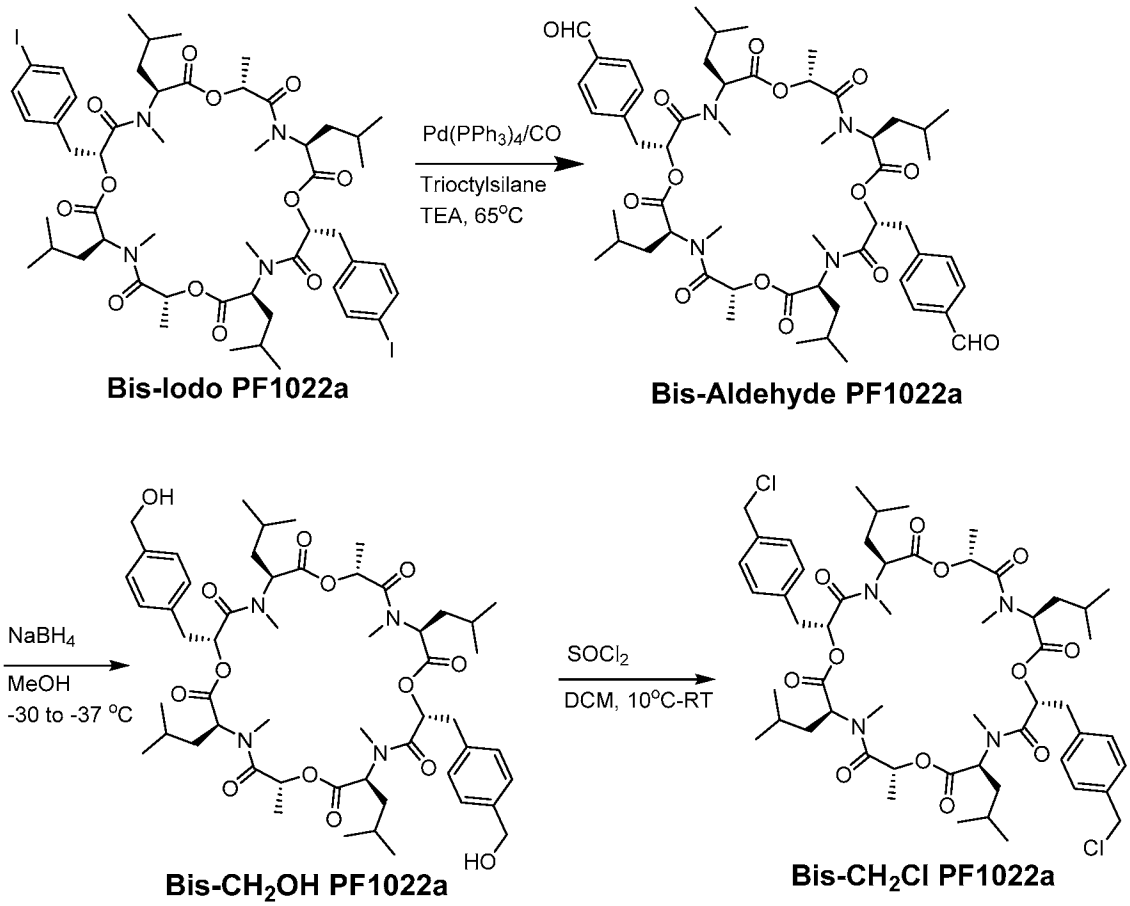
Step 1:

C1 (151.5g, 0.138mol) was added in portions to a 33% solution of HBr in acetic acid (750mL) and stirred at 35°C for 6.5 hours. The reaction mixture was cooled to 15°C (ice/water bath) and ice/water (1.75L) was added. A solution of 10% sodium carbonate was added carefully (about 2.5L) to basify the mixture to pH 4-5. The mixture was extracted with ethyl acetate (2L). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (2x1.5L), and brine (1L). The organic layer was dried over Na_2SO_4 and evaporated to a crisp foam (143g). The foam was recrystallised from 2-propanol (600mL) and dried to leave the product, C1-1, as a free flowing white powder (117.0g, 87% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.99 (m, 4H), 6.58 (m, 4H), 4.4-5.6 (m, 8H), 3.62 (br s, 4H), 2.7-3.1 (m, 16H), 1.16-1.9 (m, 14H), 0.73-1.1 (m, 28H). UPLC (Long acid 2-95%): 2.79 min, 980.3 Da $[M+H]^+$.

Step 2:

To a solution of C1-1 (10g, 10.2mmol) in CH_3CN (125mL) and added pTSA (7.1g, 40.8mmol, 4.0eq) at room temperature and then cooled to -2°C using ice-salt bath. A 1.5M solution of $NaNO_2$ (1.70g, 24.5mmol, 2.4eq) in water (15mL) was slowly added over a period of 7 minutes while maintaining temperature around -1°C. After 15 minutes, CuI (8.7g, 46.0mmol, 4.5eq) was added over 5 minutes and rinsed with water (20ml). Resulting brown mixture was stirred at about -1ºC for 30 minutes, and then stirred at about -2 to 5°C for 30 minutes without cooling. Reaction was cooled to 2°C by adding ice into reaction and quenched with 25% sodium thiosulphate solution (100mL). Organic layer was separated and aqueous layer extracted with ethyl acetate (2x75ml). Combined organic solution was washed with water (100mL) and saturated $NaHCO_3$ (75mL), brine (100mL), dried over Mg_2SO_4 and concentrated under vacuum to get solid 16g. Obtained solid dissolved in DCM (30mL), adsorbed on silica gel (60g) and filter through silica gel bed (100g) using 50% EtOAC/hexane. Organic solution was concentrated under vacuum to a solid and dried under vacuum at 40°C for overnight to get Bis-Iodo PF1022a, (7.5 g, 62 %). 1H NMR (600 MHz, CDCl3) δ: 0.68-0.98 (m, 29H), 1.24-1.7 (m, 13 H), 2.67-3.07 (m, 16 H), 4.36-4.43 (m, 1H), 4.96-5.63 (m, 7 H), 6.98-7.05 (m, 4H), 7.60-7.69 (m, 4H). LC-MS (*m/z*): [M+] = 1200

Scheme 1c: Route for Preparation of Bis-CH_2Cl PF1022a:



As shown in Scheme 1c, conversion of Bis-Iodo PF1022a to Bis-CH_2Cl PF1022a is accomplished by a three step sequence. Palladium catalyzed carbonylation in an atmosphere of carbon monoxide to install the aldehyde that is then reduced with a hydride reagent to form Bis-CH_2OH PF1022a can readily be converted using standard chlorinating agent to the Bis-CH_2Cl PF1022a intermediate. In the preparation of Bis-Aldehyde PF1022a a small but appreciable amount (2%-20%) of 4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzaldehyde (Mono-Aldehyde PF1022a) is also formed. Mono-aldehyde PF1022a may be separated from Bis-Aldehyde PF1022a using standard reverse phase HPLC methods. Bis-CH_2Cl PF1022a was used as a starting material, with an appropriate Het, to prepare some of the examples of Formula 1 presented in Tables 1-2, 6, 9, and 10 using conditions described in step 2 of Scheme 2.

Synthetic Procedures for the Preparation of Bis-CH_2Cl PF1022a (Scheme 1c):

Step 1:

A 2L pressure reactor was charged with Bis-Iodo PF1022a (130.0g, 101.7mmol), $HSi(octyl)_3$ (225g, 610.1mmol), DMF (700mL), TEA (131mL, 938.8mmol) and $Pd(TPP)_4$ (5.6g, 4.8mmol) and then purged with nitrogen and carbon monoxide. Reaction was heated to 65°C under carbon monoxide (55 psi) and stirred for 2 hours. Reaction was cooled to 22°C, slowly diluted with ice-water (2.5 L). Solid was collected, washed with water (2x250 mL) hexane (2x200 mL) and dried under vacuum at 50°C for overnight to get crude Bis-Aldehyde PF1022a as light brown solid (130g).

Step 2:

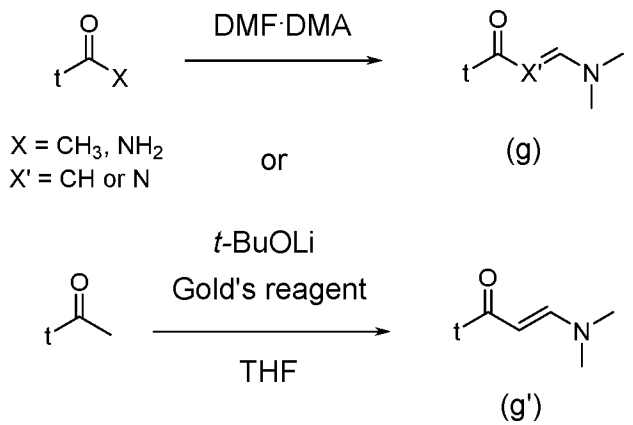
A 3L round bottom flask charged with crude Bis-Aldehyde PF1022a (130 g) and methanol (1100 mL) and then cooled to -35°C using acetonitrile/dry-ice bath. To the mixture was slowly added $NaBH_4$ (5.0g, 130mmol) while maintaining temperature below -30°C and stirred between -35 and -37°C for 1 hour. Reaction was slowly quenched with saturated NH_4Cl (100mL), brought to 10°C and concentrated to approximately 3/4 volume under vacuum at 40°C. Mixture was diluted with water (150 mL), extracted with ethyl acetate (3x 150 mL). Organic solution was dried over $MgSO_4$, filtered and concentrated under vacuum at 45°C to a dark brown solid. Solid was heated in 1:2 mixture of EtOAC/Hexane (200 ml) at 60°C and stirred at room temperature for 4 hours. Solid was collected, washed with 25% ethyl acetate in hexane (2x 50 mL), hexane (50 mL) and dried under vacuum to get Bis-CH_2OH PF1022a (103.5 g, 91% yield for 2 steps). 1H NMR (600 MHz, $CDCl_3$) δ: 0.75-1.17 (m, 26H), 1.23-1.96 (m, 16H), 2.70-2.92 (m, 9H), 3.01-3.23 (m, 7H), 4.45-4.53 (m, 1H), 4.65-4.74 (m, 4H), 5.03-5.14 (m, 1H), 5.19-5.72 (m, 6H) 7.20-7.36 (m, 8H). LC-MS (*m/z*): [M+H] = 1009 and [(M+23] = 1031

Step 3:

A 1L 3 neck round bottom flask was charged with Bis-CH_2OH PF1022a (98g, 90.30 mmol) and DCM (300mL) and then cooled to 10°C with external ice-water bath. Thionyl chloride (25 ml, 343.2 mmol) was added over 7 minutes, cooling bath removed and mixture stirred at room temperature. After 1 hour, reaction was concentrated under vacuum at 35°C to a syrup, diluted with heptane (2x 75 mL) and concentrated to a solid. Brown solid was dissolved in ethyl acetate (250 ml) and

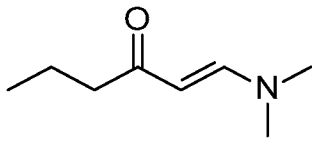
washed with aqueous Na_2CO_3 (150 mL) (50 mL saturated Na_3CO_3 solution diluted with water (100 mL) to pH 7.8. Organic layer was separated and aqueous layer extracted with ethyl acetate (2x100 mL). Combined organic solution was dried over $MgSO_4$, and concentrated under vacuum to a brown solid. Crude product in ethyl acetate (300 ml) was stirred with activated carbon (12g) for 4 hours at room temperature, filtered through celite bed and concentrated to solid. Obtained crude material in MTBE (110 mL) was heated to reflux, diluted with hexane (50 ml) and stirred at room temperature for overnight. Solid was collected, washed with 20% MTBE/hexane (50mL), hexane (50mL) and dried under vacuum at 50°C to get $BisCH_2Cl$ PF1022a as off-white solid (98 g, 98% yield). 1H NMR (600 MHz, CDCl3) δ: 0.75-1.17 (m, 26H), 1.25-1.95 (m, 16H), 2.70-2.90 (m, 9H), 3.04-3.26 (m, 7H), 4.44-4.57 (m, 1H), 4.54-4.62 (m, 4H), 5.05-5.13 (m, 1H), 5.24-5.74 (m, 6H) 7.20-7.39 (m, 8H). LC-MS (*m/z*): [M+H] = 1045, [M+2] = 1046, [M+3]= 1047 and [M+4]=1047.

Scheme 1d.



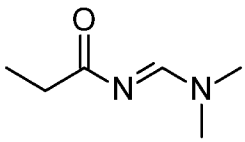
As shown in Scheme 1d, in addition to commercially available enaminones, intermediates (g ang g') can be prepared by reacting purchased methyl ketone or amide monomers with N,N-dimethylformamide dimethyl acetal (DMF·DMA); or by using a non-nucleophilic base such as lithium tert-butoxide (*t*-BuOLi) with an aminomethylene electrophile equivalent such as Gold's reagent (*Tetrahedron*, 2017 3643-3651). Intermediates (g and g') can further be used in a cyclization reaction (Scheme 3) to obtain Formula 1A1-1 and 1F1 compounds. The variable "t" is as described in Scheme 3.

The following procedure was used in accordance with Scheme 1d to prepare intermediate (E)-1-(dimethylamino)hex-1-en-3-one for preparing e.g., Example 1b-205



To a solution of lithium tert-butoxide (26mL of a 1.0M solution) in THF (25 mL) was added dropwise pentan-2-one (2.0g, 23.0 mmol). The reaction was stirred at room temperature for 30 min and Gold's reagent (4.3g, 26.0 mmol) was added. The reaction mixture was heated to reflux for 18 hours and cooled to room temperature. Next, the crude mixture was diluted with sat. ammonium chloride and extracted with chloroform (2 x 100mL). The organic phase was dried (sodium sulfate) and concentrated under vacuum to afford intermediate 2l (2.6g, 79%) as an oil. LC-MS (*m/z*): [M+H] = 142.

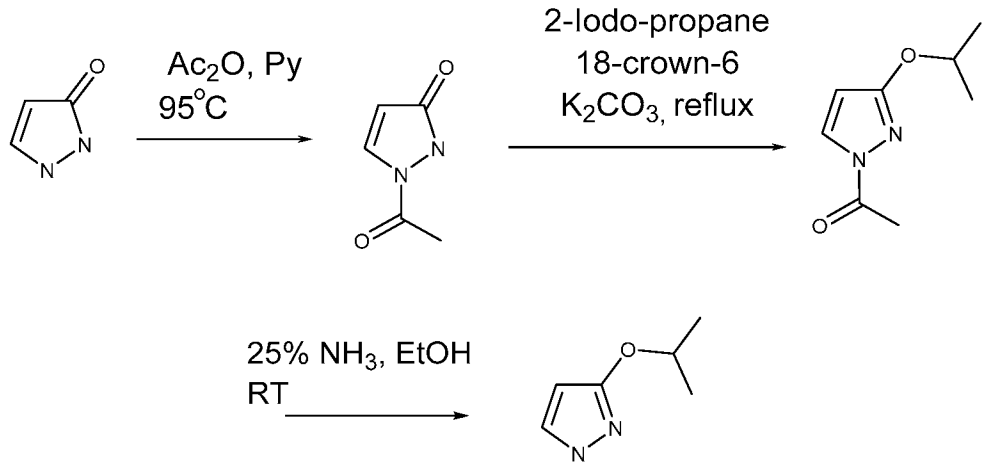
The following procedure was used in accordance with Scheme 1d to prepare intermediate (E)-N-((dimethylamino)methylene)propionamide, for preparing e.g., Example 9-50



To a solution of propanamide (1g, 8.2 mmol) in toluene (30mL) was added DMF·DMA (1.9mL, 14.0 mmol). The reaction was heated to 100°C for 18 hours and cooled to room temperature. The crude reaction was concentrated under vacuum to afford intermediate 3l (1.6g, 91%). LC-MS (*m/z*): [M+H] = 129.

Preparation of Other Intermediates that can be used to prepare examples of Formula 1a-1f in accordance with step 2 of Scheme 2.

Scheme 1e: Preparation of intermediate 3-isopropoxy-1H-pyrazole for preparing e.g., Example 1b-151

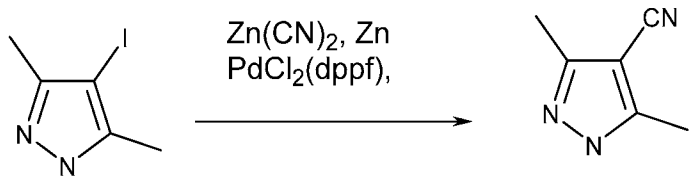


Step 1. A solution of 1,2-dihydro-pyrazol-3-one (4.50 g, 53.57 mmol) in pyridine (13.5 mL) was heated to 95°C and a solution of acetic anhydride (5.57 mL, 58.93 mmol) in pyridine (13.5 mL) was added over 10 minutes and continued heating for additional 3 hours. The reaction mixture was concentrated in vacuo and triturated with 10% ether-pentane to get 1-acetyl-2,3-dihydro-1H-pyrazol-3-one (5.4 g, 80%) as white solid.

Step 2. To a stirred solution of 1-acetyl-2,3-dihydro-1H-pyrazol-3-one (1.0 g, 7.93 mmol) in acetonitrile (20 mL) were added K_2CO_3 (2.19 g, 15.86 mmol), 18-crown-6 (0.06 g, 0.24 mmol) followed by the addition of 2-iodopropane (1.752 g, 10.31 mmol) drop wise at room temperature. Resulting reaction mixture was heated to reflux for 5 hours. After completion, the reaction mixture was quenched with water and extracted with 10% methanol in dichloromethane. Combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Crude compound was purified by column chromatography (5-10% ethyl acetate in hexane) to get 1-[3-(propan-2-yloxy)-1H-pyrazol-1-yl]ethan-1-one (800 mg, 60%) as yellow liquid. MS (ESI): m/z 169.1 $[M+1]^+$.

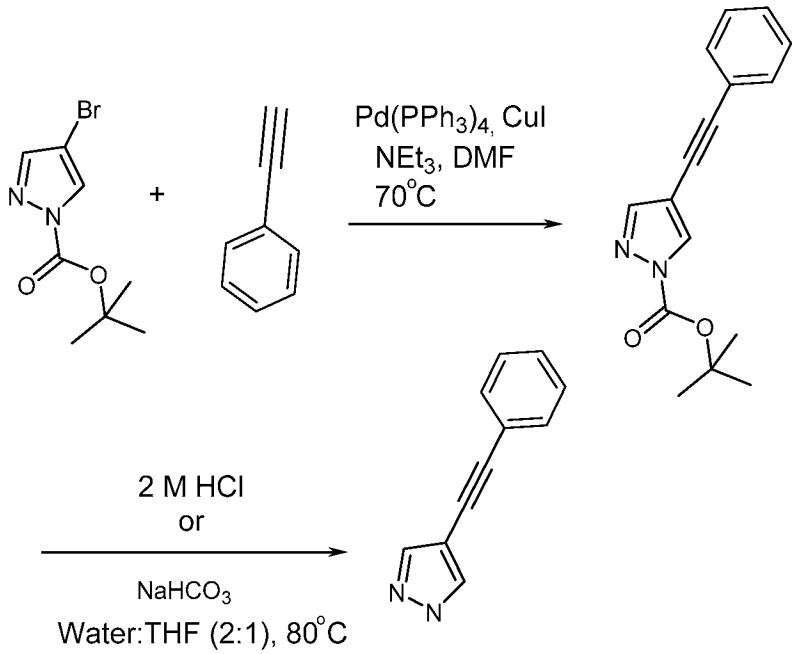
Step 3. To a stirred solution of 1-(3-Isopropoxy-pyrazol-1-yl)-ethanone (100 mg, 0.60 mmol) in ethanol (1 mL) was added aqueous ammonium hydroxide (1 mL) at 0°C and resulting mixture was stirred at RT for 1 hour. After completion, the reaction mixture was concentrated under reduced pressure and azeotroped with toluene and triturated with pentane to get 3-(propan-2-yloxy)-1H-pyrazole (45 mg, 60%) as yellow liquid. MS (ESI): m/z 126.9 $[M+1]^+$.

Scheme 1f: Preparation of intermediate 3,5-dimethyl-1H-pyrazole-4-carbonitrile for preparing e.g., Example 1b-117



To a stirred degassed solution of 4-iodo-3,5-dimethyl-1H-pyrazole (500 mg, 2.25 mmol) in DMF (5 mL) was added $Zn(CN)_2$ (141.2 mg, 1.58 mmol) followed by $Pd(dppf)Cl_2$ (82.4 mg, 0.11 mmol) and Zn-dust (7.4 mg, 0.11 mmol) under inert atmosphere. Resulting mixture was heated at 100°C for 4 hours. After completion, the reaction mixture was diluted with cold water and extracted with ethyl acetate. Combined organic layer was washed with water, brine, dried over sodium sulphate, filtered, and concentrated under reduced pressure. Crude compound was purified by column chromatography (30%-50% ethyl acetate-hexane) to afford 3,5-dimethyl-1H-pyrazole-4-carbonitrile (120 mg, 44%) as light brown solid.

Scheme 1g: Preparation of intermediate 4-(phenylethynyl)-1H-pyrazole for preparing e.g., Example 1b-102

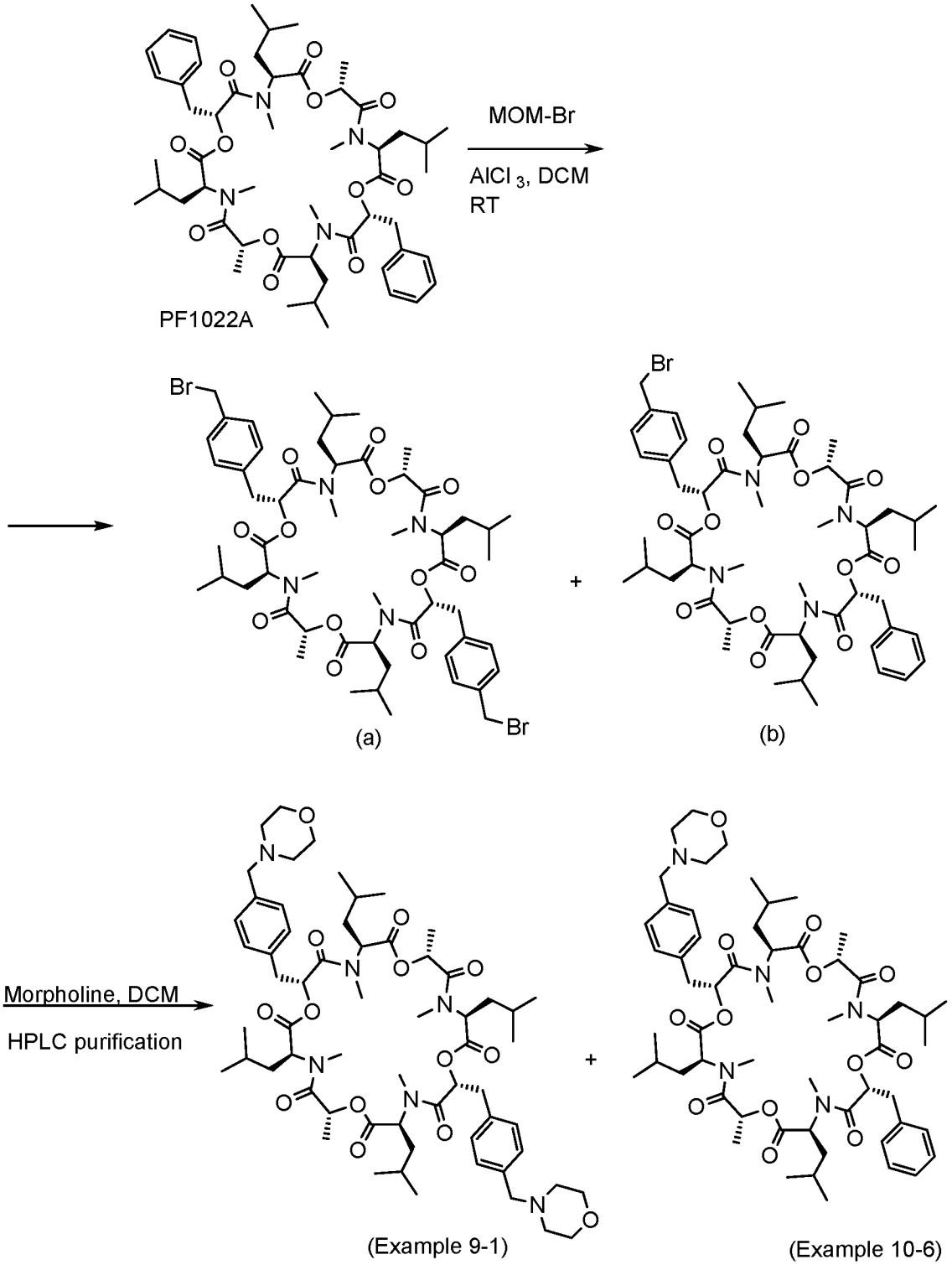


Step 1. To a stirred degassed solution of 4-bromo-pyrazole-1-carboxylic acid tert-butyl ester (300 mg, 1.21 mmol) in DMF (3 mL) were added phenyl acetylene (0.24

mL, 2.18 mmol), triethyl amine (0.84 mL, 6.05 mmol), CuI (40.16 mg, 0.24 mmol) followed by $Pd(PPh_3)_4$ (279.58 mg, 0.24 mmol). Resulting reaction mixture was heated at 70°C for 6 hours. After completion, the reaction mixture was diluted with water and extracted with ethyl acetate. Combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. Crude compound was purified by column chromatography (10-20% ethyl acetate in hexane) to get tert-butyl 4-(2-phenylethynyl)-1H-pyrazole-1-carboxylate (230 mg, 70%) as brown liquid. MS (ESI): m/z 269.3 $[M+1]^+$.

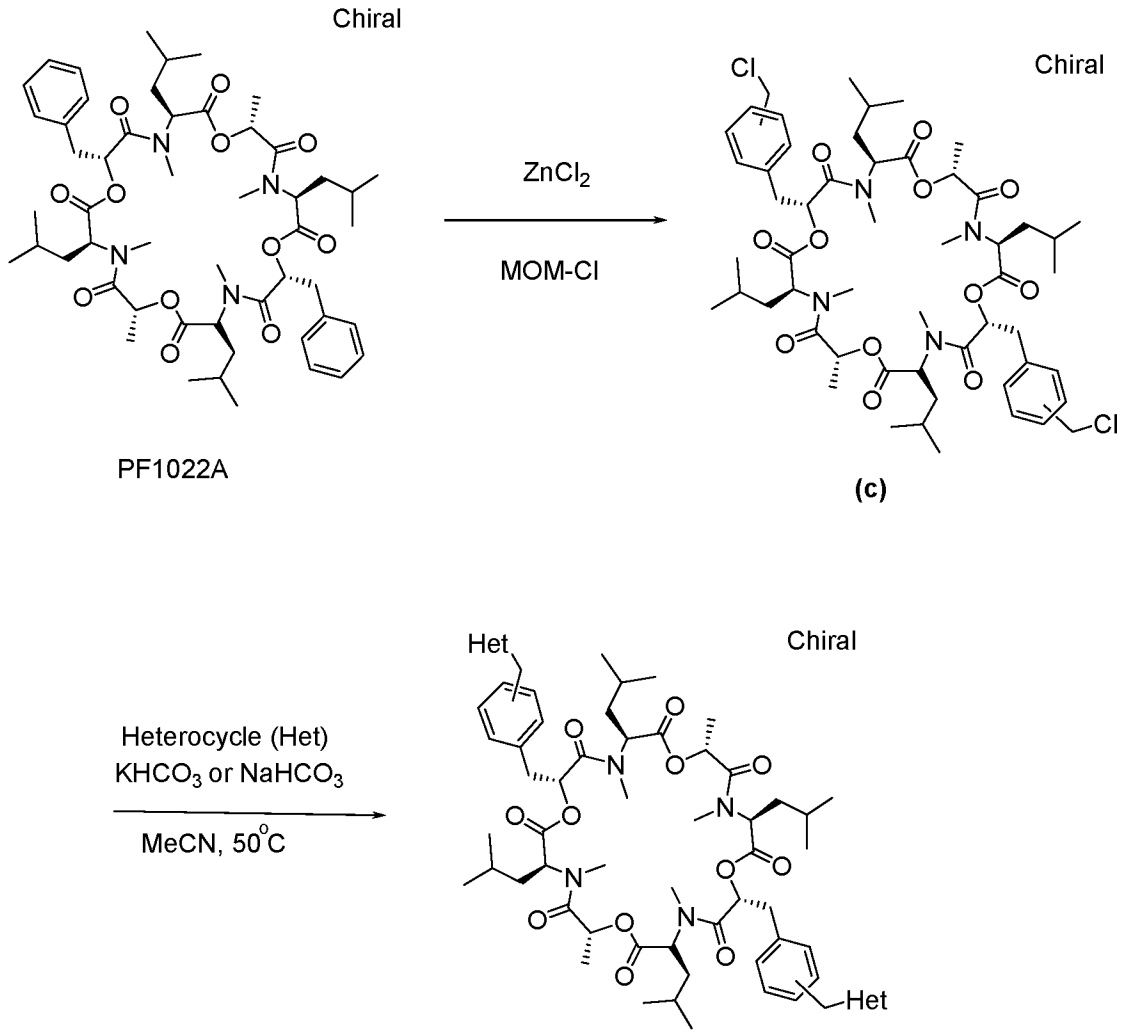
Step 2. To a stirred solution of tert-butyl 4-(2-phenylethynyl)-1H-pyrazole-1-carboxylate (2.3 g, 8.58 mmol) in DCM (5 mL) at 0°C, 2M HCl in ether (10 mL) was added drop wise and stirred at RT for 16 hours. After completion, the reaction mixture was concentrated under reduced pressure and co-distilled with pentane (2 X 10 mL). The crude was further triturated with 10% ethyl acetate in hexane (2 times) to afford 4-(2-phenylethynyl)-1H-pyrazole (950 mg, 54%, HCl salt) as pale brown solid. MS (ESI): m/z 169.1 [M+1]+.

Scheme 1

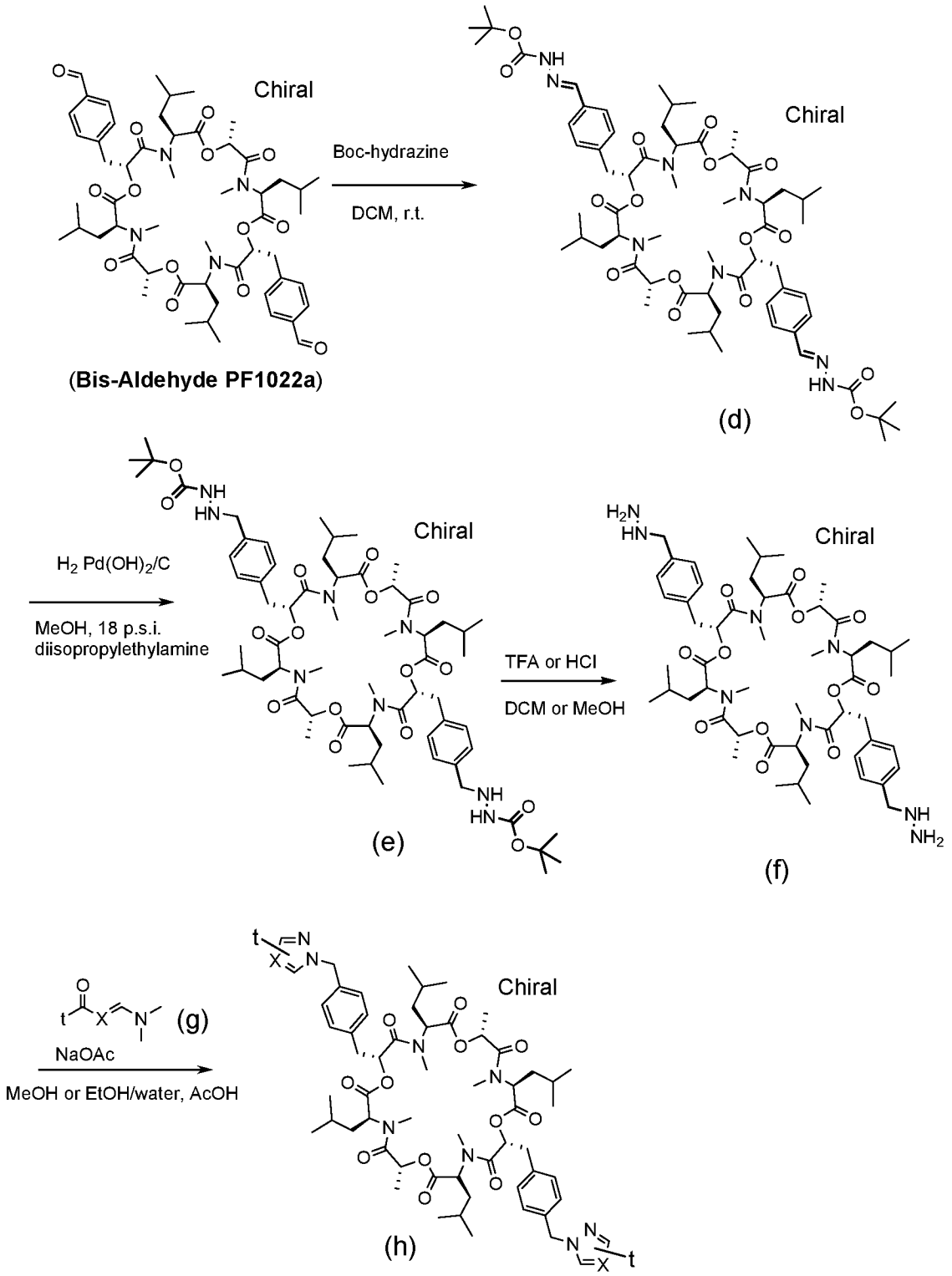

MOM-Br
AlCl 3, DCM
RT
PF1022A
Br
Br
Br
(a)
(b)
Morpholine, DCM
HPLC purification
(Example 9-1)
(Example 10-6)

The het (heterocycle or heteroaryl) compounds in Schemes 1 and 2 were prepared by reacting commercially available PF1022A with either MOM-Cl or MOM-Br in the presence of a lewis acid such as $ZnCl_2$ or $AlCl_3$ to afford a regio-mixture (including mono-hybrids) of halomethyl intermediates. The regio-mixture was subsequently treated with an appropriate het in the presence of base such as $NaHCO_3$ or $KHCO_3$ and solvent such as acetonitrile to afford a mixture of products. The crude mixture was purified using reverse-phase HPLC to afford single regio-isomers and mono-hybrid compounds of Formula 1 (*i.e.*, 1A1-1, 1A1-2, 1B1-1, 1B1-2, 1C1-1, 1C1-2, 1D1-1, 1E1, 1F1, and 1F2).

Scheme 2:



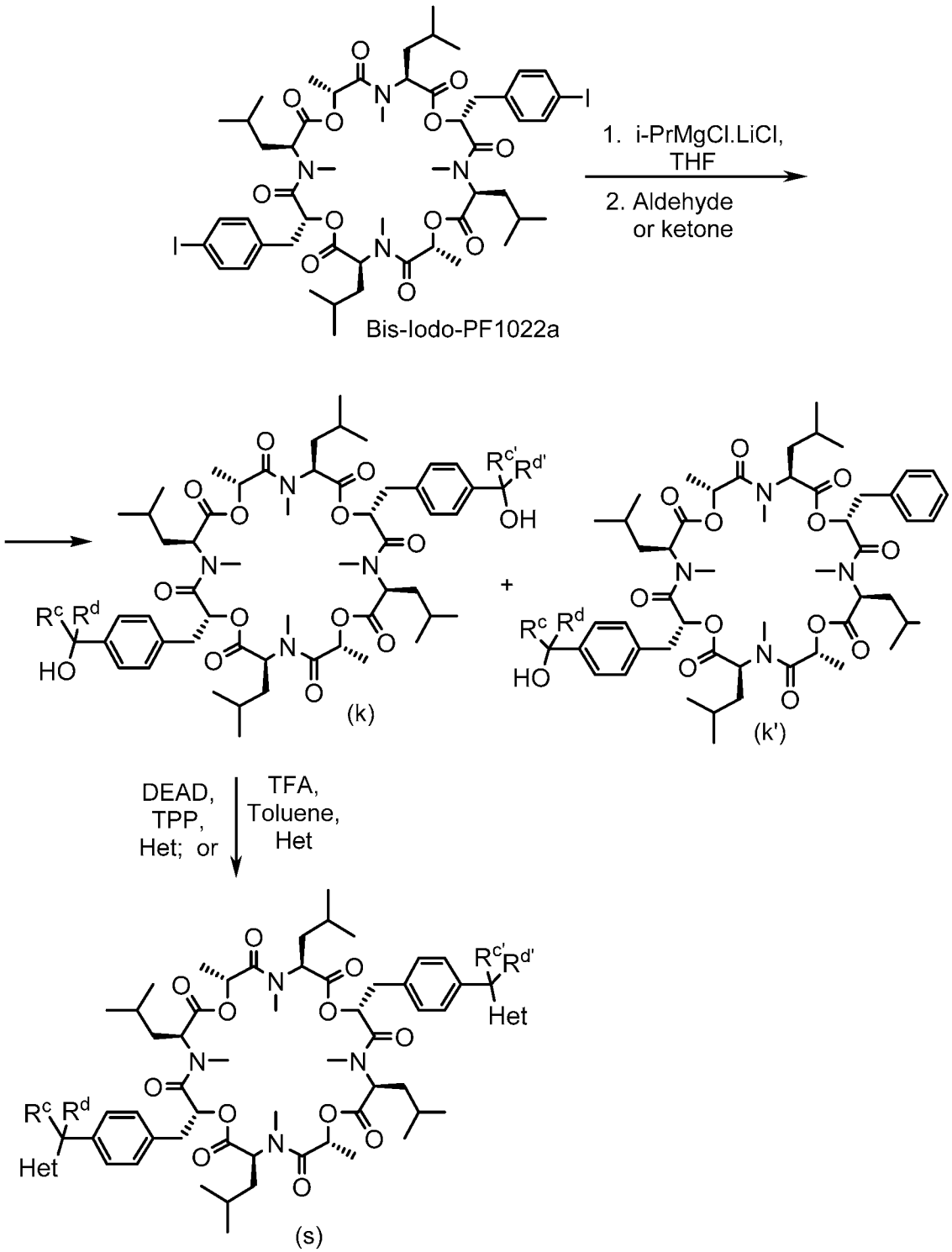
Scheme 3:



As shown in Scheme 3, the following intermediate (d) was generated from the appropriate starting bis-aldehyde PF1022a using boc-hydrazine in a non-polar

aprotic solvent such as DCM or DCE. The hydrazone intermediate can subsequently be reduced to the corresponding hydrazine (e) with hydrogen gas using a palladium catalyst such as Pd/C or $Pd(OH)_2/C$ in a protic solvent such as MeOH or EtOH and base such as TEA or diisopropylethylamine. The boc-intermediate (e) can be deprotected to afford the intermediate (f) with an acid source such as TFA or HCl. Examples found in Table 1b can be synthesized from intermediate (f) in a condensation reaction using the appropriately substituted enaminone (g and g') or aminoacetamide (g) from Scheme 1d to provide compound (h). The variable "X" in Scheme 3 represents C or N. The variable "t" of the L1 and L2 heteroaryl ring represents any heteroaryl substitution as defined herein. The major regio-isomers are 5' and the minor isomer at 3'. Examples of Formula (1A1-1, i.e., wherein X is C) and Formula (1F1, i.e., wherein X is N) can be prepared according to this scheme.

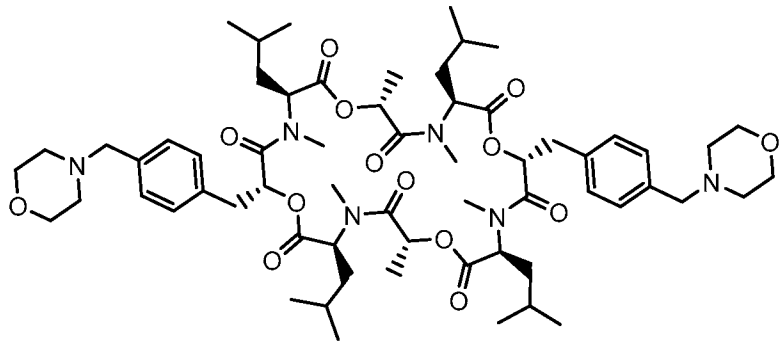
Scheme 4:



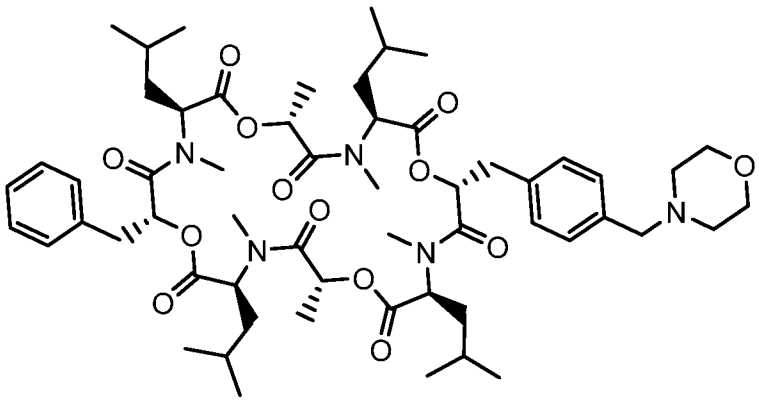
As shown in Scheme 4, the following tertiary alcohol intermediates (k and k') were generated from the starting bis-iodo PF1022a compound using a Grignard

reagent such as iPrMgCl·LiCl followed by addition of an appropriate electrophile. The tertiary alcohol intermediates can be subsequently converted to the Formula (s) compounds which correspond to at least Formula (1A1-3; wherein Het is pyrazole) compounds via acidic conditions using TFA and toluene, or by Mitsunobu conditions with TPP and DEAD.

The following procedures were used in accordance with Scheme 1 to prepare the emodepside analog (methylene linked morpholine), which results in the bis-para analog (Example 9-1) and the mono-para analog (Example 10-6). The mono-para analogs are synonomously described herein as hybrid analogs.



(9-1)



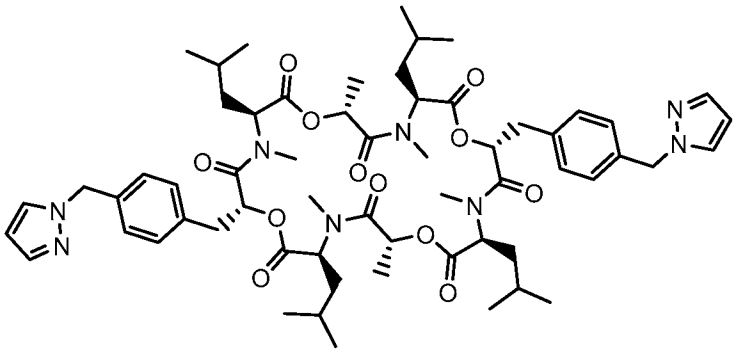
(10-6)

Step-1: To ice-cooled suspension of $AlCl_3$ (2 g, 15.0 mmol) in CH_2Cl_2 (5 mL) were slowly added a solution of PF1022A (1.00 g, 2.05 mmol) in CH_2Cl_2 (5 mL) and bromomethyl methyl ether (2.0 mL, 24.5 mmol), and then mixture stirred at room temperature for 17 hours. The reaction mixture was poured into ice-water (50 mL) and extracted with ethyl acetate (3x25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2x25 mL) and brine (25 mL), dried over Na_2SO_4 and

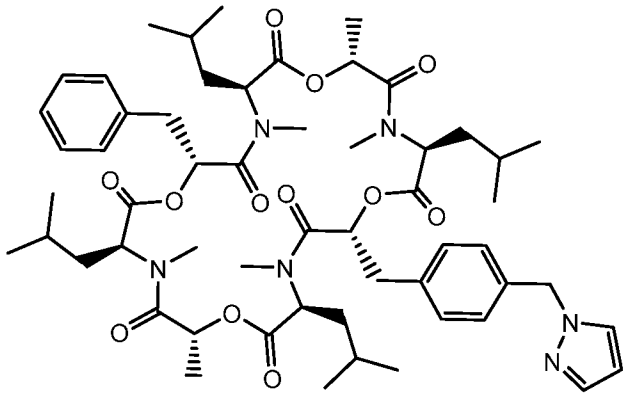
concentrated to get mixture of un-separable intermediates (a) and (b) (1.0 g). LC-MS (*m/z*): [M+H] = 1133 for intermediate (a) and LC-MS (*m/z*): [M+H] = 1041 for intermediate (b).

Step-2: To a solution of mixture of crude bromomethyl intermediates (a) and (b) (150mg,) in CH_2Cl_2 (3mL) was added morpholine (0.1 mL) and stirred at room temperature for 5 hours. The reaction mixture was diluted with EtOAc(10 mL), washed with water (5 mL), brine, dried (Na_2SO_4), and concentrated under vacuum. The crude material was purified using reverse phase (Kinetex 5uM EVO C18 100A LC column 250 x 30.0mm) eluting from 10% (MeCN/water, 0.1%TFA) to 100%, (MeCN, 0.1%TFA) over 20 minutes collecting 2 peaks. Fractions were lyophilized to afford Example 9-1 (28 mg) and Example 10-6 (11mg).

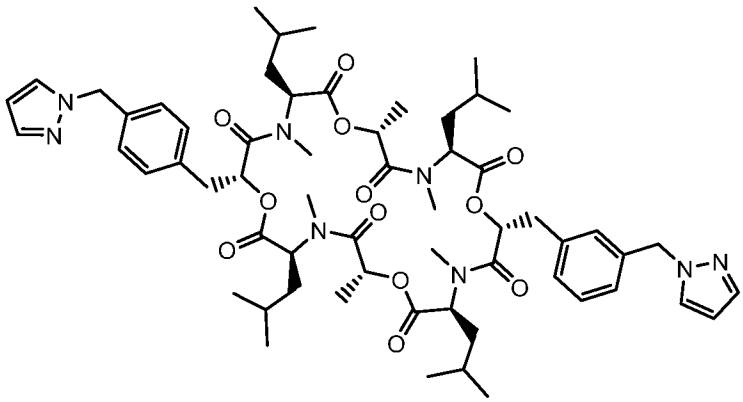
The following procedures were used in accordance with Scheme 2 to prepare representative pyrazole analogs of Formula (1); wherein Het is pyrazole (e.g., 1b-23, 2-1, and 3-1). The mono-para analogs are synonomously described herein as hybrid analogs.



(1b-23)



(2-1)



(3-1)

Step 1. PF1022A (2000mg, 2.10mmol) was dissolved in MOM-Cl (60mL, 30vol) while stirring and zinc chloride (2.3g, 16.9mmol) was next added. The stirring was continued at room temperature for 48 hours. The crude reaction was concentrated under vacuum, dissolved in EtOAc (150mL) and washed with water and brine. The organic phase was subsequently dried (Na_2SO_4) and concentrated under vacuum to afford intermediate (c) as a mixture of regio-isomers (2.34g, 106%). LC-MS (*m/z*): [M+] = 1046.

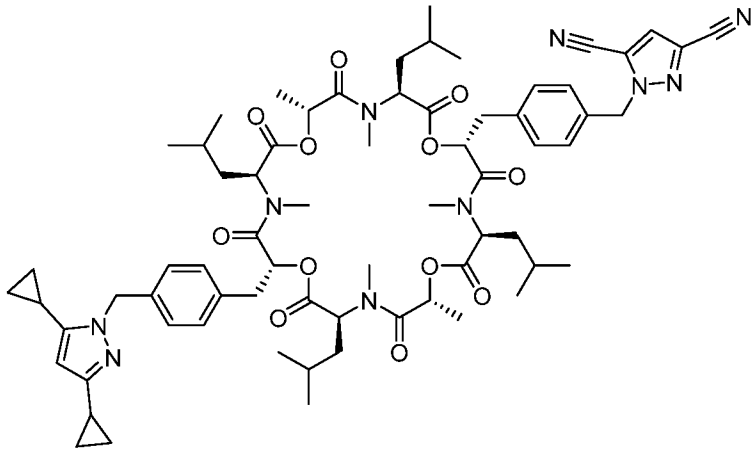
Step 2: To a solution of chloromethyl intermediate (c) (120mg, 0.11mmol) in MeCN (5mL) was added 1H-pyrazole (47mg, 0.69mmol), NaHCO3 (60mg, 0.69mmol) and KI (75mg, 0.46mmol). The reaction mixture was stirred at 50°C under N_2 for 18 hours. Next, the reaction mixture was diluted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude material was purified using reverse phase (Kinetex 5uM EVO C18 100A LC column 250 x 30.0mm) eluting from 50,50,0.1% (MeCN,water,TFA) to 100, 0.1% (MeCN, TFA) over 20 minutes

collecting 3 major peaks. Fractions were lyophilized to afford Example 1b-23 (18mg, 14%), Example (2-1) and Example 3-1 (13mg, 10%).

Additionally, other compounds were similarly prepared using MOM-Cl, for example; Examples 9-4, 9-5, 9-6, 9-7, 9-8, 9-9, 9-10, 10-3, 10-5, 10-6, 10-7, and 10-8.

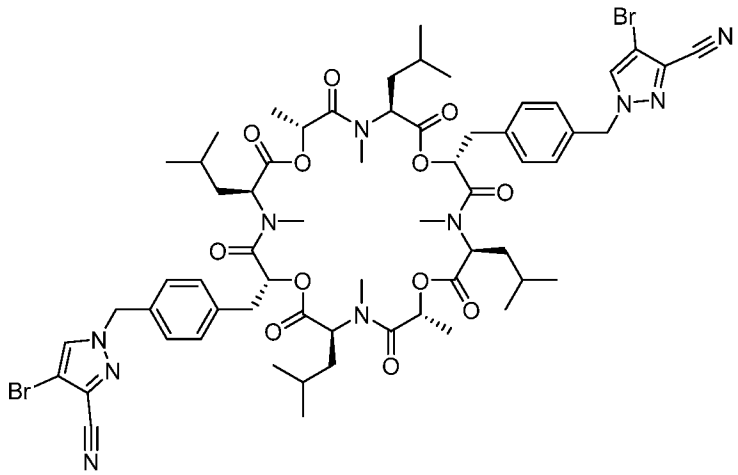
Representative Examples were also prepared according to Scheme 2; for example: Examples 9-13 and 10-4 were synthesized following the same procedure as for Example 1b-23, but using 1H-1,2,4-triazole in place of 1H-pyrazole in Step 2. Examples 1b-24, 2-2, and 3-2 were synthesized following the same procedure as for Example 1b-24, but using 4-methyl-1H-pyrazole in place of 1H-pyrazole. Examples 1b-25 and 3-3 were synthesized following the same procedure as for Example 1b-23, but using 4-bromo-1H-pyrazole in place of 1H-pyrazole. Examples 6-1, 7-1, and 8-1 were synthesized following the same procedure as for Example 1b-23, but using 2-methyl-1H-imidazole in place of 1H-pyrazole. Examples 1b-26, 2-3, and 3-4 were synthesized following the same procedure as for Example 1b-23, but using using 4-phenyl-1H-pyrazole in place of 1H-pyrazole. Examples 1b-27, 2-5, and 3-6 were synthesized following the same procedure as for Example 1b-23, but using using using 4-fluorophenyl-1H-pyrazole in place of 1H-pyrazole; and 4-chlorophenyl-1H-pyrazole in place of 1H-pyrazole for compounds 1b-28, 2-6, and 3-7. Examples 1b-29 and 2-7 were synthesized following the same procedure as for Example 1b-23, but using using 3,5-dimethyl-1H-pyrazole in place of 1H-pyrazole. Examples 6-2 and 8-2 were synthesized following the same procedure as for Example 1b-23, but using using 1H-imidazole in place of 1H-pyrazole. Examples 1b-30, 2-8, and 3-9 were synthesized following the same procedure as for Example 1b-23, but using using 4-tert-butyl-1H-pyrazole in place of 1H-pyrazole; and Examples 1b-31, 2-9, and 3-10 using 4-ethyl-1H-pyrazole in place of 1H-pyrazole. Examples 6-3, 7-3, and 8-3 were synthesized following the same procedure as for Example 1b-23, but using using 2-bromo-1H-imidazole in place of 1H-pyrazole; Examples 6-4, 7-4, and 8-4 using 2-ethyl-1H-imidazole in place of 1H-pyrazole; and Examples 6-6 and 8-6 using 2-tert-butyl-1H-imidazole in place of 1H-pyrazole. Examples 6-7, 7-7, and 8-7 were synthesized following the same procedure as for Example 1-37, but using using 2-cyclopropyl-1H-imidazole in place of 1H-pyrazole.

Examples 1a-13, 1b-93, and 2-65 were prepared from intermediate Bis-CH_2Cl PF1022a (schemes 1a-c) according to the conditions in step 2 of Scheme 2.



(1a-13)

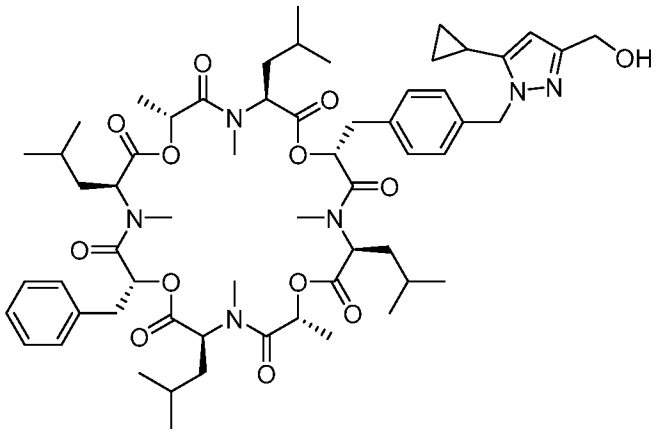
was prepared: to a solution of Bis-CH_2Cl PF1022a (120 mg, 0.11 mmol) in acetonitrile (5.7mL, 0.02M) was added 3,5-dicyclopropyl-1H-pyrazole (25. 5 mg, 0.17 mmol, 1.5 equivalents), potassium bicarbonate (45.9 mg, 0.45 mmol) and potassium iodide (114mg, 0.69 mmol). The mixture was heated to 50°C for 18 hours. 1H-pyrazole-3,5-dicarbonitrile (34 mg, 0.28 mmol) was added and the mixture heated to 50°C for 18 hours. After allowing cooling to room temperature, the solvent was removed under reduced pressure and the residue partitioned between water and DCM. The organics were separated, dried over $MgSO_4$ and evaporated. The crude material was purified by reverse phase HPLC to give the title product as a white solid (30mg, 21%).



(1b-93)

was prepared: to a solution of Bis-CH_2Cl PF1022a in acetonitrile (4.8 mL, 0.02M) was 4-bromo-1H-pyrazole-3-carbonitrile added (66 mg, 0.38 mmol), potassium

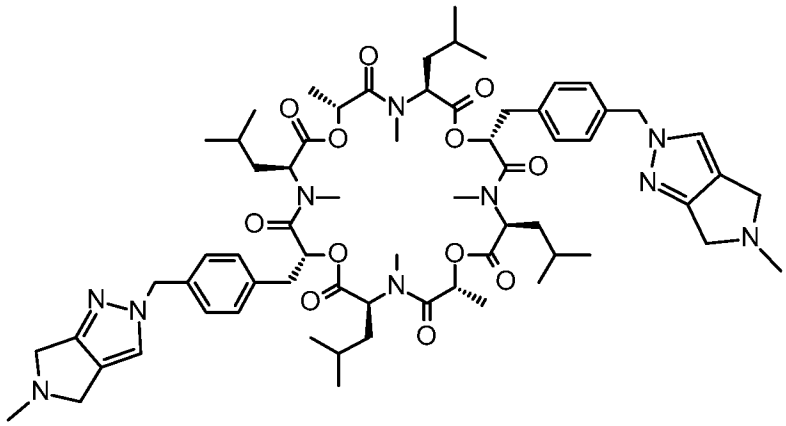
bicarbonate (38 mg, 0.38 mmol) and potassium iodide (95 mg, 0.57 mmol). The mixture was heated to 50°C for 48 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue partitioned between water and DCM. The organics were separated, dried over $MgSO_4$ and evaporated. The crude material was purified by reverse phase HPLC to give the title product as a white solid (46 mg).



(2-65)

was prepared: to a solution of mono-CH_2Cl PF1022a (120 mg, 0.12 mmol) in acetonitrile (6 mL, 0.02M) was added (5-cyclopropyl-1H-pyrazol-3-yl)methanol (33 mg, 0.24 mmol), potassium bicarbonate (24 mg, 0.24 mmol) and potassium iodide (59 mg, 0.36 mmol). The mixture was heated to 50°C for 48 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue partitioned between water and DCM. The organics were separated, dried over $MgSO_4$ and evaporated. The crude material was purified by reverse phase HPLC to give the title product as a white solid (49 mg, 37 %).

The following procedures were used in accordance with Scheme 2 to prepare Example 9-47.



(9-47)

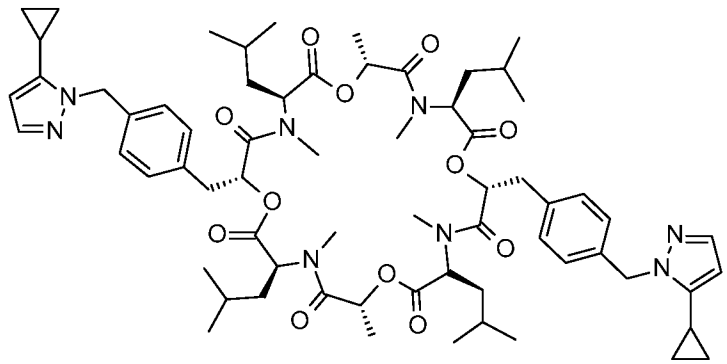
Step 1: To a stirred solution of Bis-CH_2Cl PF1022a (150 mg, 0.14 mmol) in acetonitrile (6 mL) were added 2,6-Dihydro-4H-pyrrolo[3,4-c]pyrazole-5-carboxylic acid tert-butyl ester (180.39 mg, 0.86 mmol), $NaHCO_3$ (72.41 mg, 0.86 mmol) and KI (95.40 mg, 0.58 mmol) at room temperature. Resulting reaction mixture was heated at 50 °C for 18 hours. After completion, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with ethyl acetate. Combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. Crude mass was purified by prep HPLC to get tert-butyl 2-[(4-{[(2R,5S,8R,11S,14R,17S,20R,23S)-14-{[4-({5-[(tert-butoxy)carbonyl]-2H,4H,5H,6H-pyrrolo[3,4-c]pyrazol-2-yl}methyl)phenyl]methyl}-4,8,10,16,20,22-hexamethyl-5,11,17,23-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl]methyl}phenyl)methyl]-2H,4H,5H,6H-pyrrolo[3,4-c]pyrazole-5-carboxylate (75 mg, 37%) as white solid. MS (ESI): m/z 1389.9 $[M-1]^-$.

Step 2. To a stirred solution of tert-butyl 2-[(4-{[(2R,5S,8R,11S,14R,17S,20R,23S)-14-{[4-({5-[(tert-butoxy)carbonyl]-2H,4H,5H,6H-pyrrolo[3,4-c]pyrazol-2-yl}methyl)phenyl]methyl}-4,8,10,16,20,22-hexamethyl-5,11,17,23-tetrakis(2-methylpropyl)-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl]methyl}phenyl)methyl]-2H,4H,5H,6H-pyrrolo[3,4-c]pyrazole-5-carboxylate (75 mg, 0.05 mmol) in DCM (1.5 mL) was added 2 M HCl in ether (0.5 mL) at 0°C. Resulting reaction mixture was stirred at room temperature for 16 hours. After completion, the reaction mixture was concentrated, and triturated

with ether to afford (3S,6R,9S,12R,15S,18R,21S,24R)-4,6,10,16,18,22-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-12,24-bis[(4-{2H,4H,5H,6H-pyrrolo[3,4-c]pyrazol-2-ylmethyl}phenyl)methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (70 mg, HCl salt, quant) as off white solid. MS (ESI): m/z 1189.7 $[M-1]^-$.

Step 3. To a stirred solution of (3S,6R,9S,12R,15S,18R,21S,24R)-4,6,10,16,18,22-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-12,24-bis[(4-{2H,4H,5H,6H-pyrrolo[3,4-c]pyrazol-2-ylmethyl}phenyl)methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone as HCl salt (60 mg, 0.05 mmol) in formic acid (4 mL), formaldehyde (30% in water, 2 mL) was added drop wise at 60°C. After addition, the reaction mixture was heated at 100°C for 2 hours. After completion, the reaction mixture was concentrated under reduced pressure. Crude compound was purified by Prep-HPLC to get example 9-47 (7 mg, 11%) as white solid. MS (ESI): m/z 1217.2 $[M-1]^-$.

As a representative example, the following procedures were used in accordance with Scheme 3 to prepare Example 1b-108.



(1b-108)

Step 1: To a solution of bis-aldehyde PF1022a (5.0g, 4.9mmol) in DCM (125mL) was added acetic acid (300uL, 5.5mmol) and tert-butyl N-aminocarbamate (1.9g, 14.9mmol). The reaction mixture was stirred at room temperature for 24 hours to afford the bis-imine intermediate (d). LC-MS (*m/z*): [M+H] = 1234.

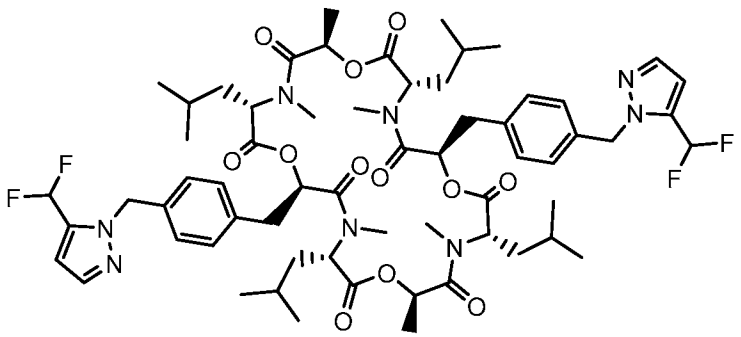
Step 2: To a solution of intermediate (d) (6.5g, 5.3mmol) in MeOH (100mL) was added $Pd(OH)_2$ (250mg, 20% on carbon) and N,N-diisopropylethylamine (3.0mL,

17.0mmol). The mixture was hydrogenated with H_2 gas at 18 p.s.i. in a Parr shaker for 1.5 h. The reaction mixture was filtered through celite and concentrated under vacuum until ~10 mL solvent remained. The crude solution was diluted with DCM (150mL) and washed with water, brine, dried (Na_2SO_4), and subsequently concentrated under vacuum to afford intermediate as (e) a solid. LC-MS (*m/z*): [M+H] = 1237.

Step 3: Intermediate (e) (2.0g, 1.6mmol) was dissolved in MeOH (75mL) and HCl gas was bubbled in for 1 minute. The reaction mixture was heated to 40 °C for 24 h. The reaction mixture was next concentrated under vacuum to afford intermediate (f) as a bis HCl salt. LC-MS (*m/z*): [M+H] = 1037.

Step 4: To a solution of intermediate (f) (450mg, 0.40mmol) in MeOH:water:AcOH (10:1:0.1, 15mL) was added commercially available 1-cyclopropyl-3-(dimethylamino)prop-2-en-1-one (225mg, 1.62mmol) and NaOAc (270mg, 3.2mmol). The reaction mixture was heated to 90 °C under microwave irradiation for 15 minutes. The crude material was purified using reverse phase (Kinetex 5uM EVO C18 100A LC column 250 x 30.0mm) eluting from 30% (MeCN/water, 0.1%TFA) to 100%, (MeCN, 0.1%TFA) over 20 minutes to afford example 1b-108 (108mg, 22%). LC-MS (*m/z*): [M+H] = 1189.

The following procedures were used in accordance with Scheme 3 to prepare Example 1b-211.



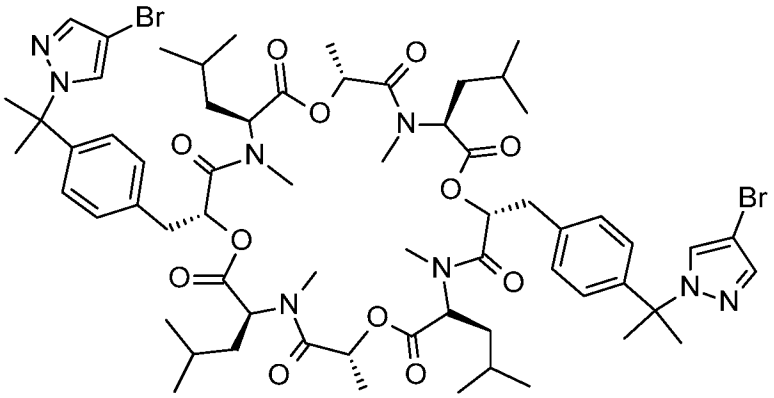
(1b-211)

Step1: To a stirred solution of bis-hydrazine (Scheme 3, intermediate (f); 1200 mg, 1.08 mmol) in MeOH:water(10:1, 25 mL) was added 4-(dimethylamino)-1,1-

dimethoxy-but-3-en-2-one (750 mg, 4.3 mmol) and NaOAc (360 mg, 4.3 mmol). The reaction mixture was stirred at room temperature for 24 hours. Next, the reaction mixture was diluted with CH_2Cl_2 (150mL) and washed with water. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The resulting crude bis-acetal (1200 mg, 0.95 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with TFA (3 mL) dropwise. The reaction was stirred at room temperature for 24 hours and concentrated under reduced pressure. The crude material was purified using reverse phase chromatography eluting from 30:70:0.1% MeCN:water:TFA to 100% MeCN:0.1% TFA over a 20 minute gradient. Fractions were lyophilized to afford 2-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[(5-formylpyrazol-1-yl)methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrazole-3-carbaldehyde (276 mg, 25%) as a solid. MS: m/z 1165 [M+H].

Step 2**:** To a stirred solution of the product of Step 1 (75 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) at -78°C was added DAST (25 µL, 0.18 mmol). The reaction was warmed to room temperature and stirred for 24 hours. The reaction was subsequently cooled to -78°C and treated with additional DAST (25 µL, 0.18 mmol). After stirring 48 hours at room temperature, the reaction was quenched with saturated $NaHCO_3$ (25 mL) and diluted with CH_2Cl_2 (25 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified using reverse phase chromatography eluting from 30:70:0.1% MeCN:water:TFA to 100% MeCN:0.1% TFA over a 20 min gradient. Fractions were lyophilized to afford example 1b-211 (11 mg, 14%) as a solid. MS: m/z 1209 [M+H].

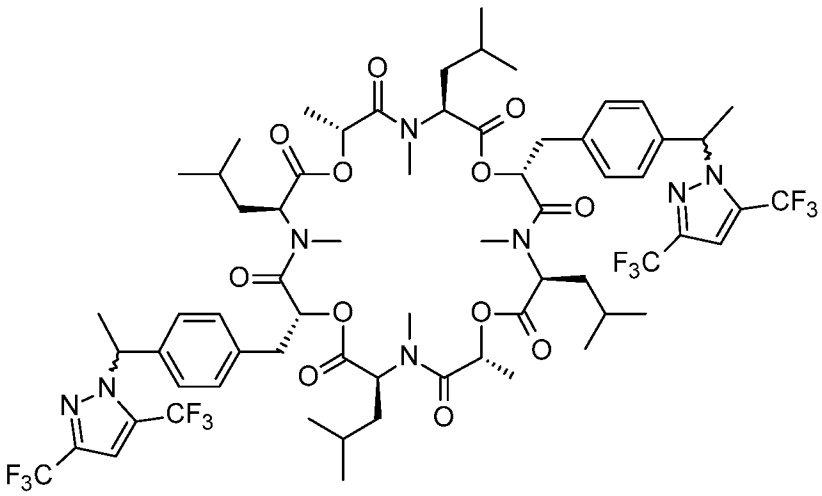
As representative examples, the following procedures were used in accordance with Scheme 4 to prepare for example: Example 1c-11 and 1c-13.



(1c-11)

Step 1. A solution of bis-iodide PF1022a (300 mg, 0.25 mmol) in dry THF (15 mL) was cooled to -78 °C and iPrMgCl.LiCl solution (1.3M in THF, 1.92 mL, 2.5 mmol) was added drop wise over a period of two minutes under argon atmosphere. Resulting mixture was warmed to -5 °C and stirred at that temperature for 20 minutes followed by addition of cold neat acetone (0.5 mL, excess) and continued stirring for additional 1h at -5°C. Reaction mixture was quenched with saturated aqueous NH_4Cl solution (2 mL) and extracted with ethyl acetate (2 x 30 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Crude mass was triturated with pentane and dried to afford compound the alcohol [310 mg, mixture of bis and mono alcohol] as white solid. It was used in the next step without further purification.

Step 2. To a stirred solution of the above mixture of alcohols (k, k'; 100 mg, 0.09 mmol) in toluene (5 mL) were added 4-bromo pyrazole (41.44 mg, 0.28 mmol) and TFA (0.03 mL, 0.38 mmol) at room temperature. Resulting reaction mixture was heated to reflux for 16 hours. After completion, the reaction mixture was diluted with water and extracted with 10% methanol in ethyl acetate. Combined organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure. Crude mass (180 mg) was purified by prep HPLC to afford the compound (1c-11) (18 mg, 14%) as white solid.

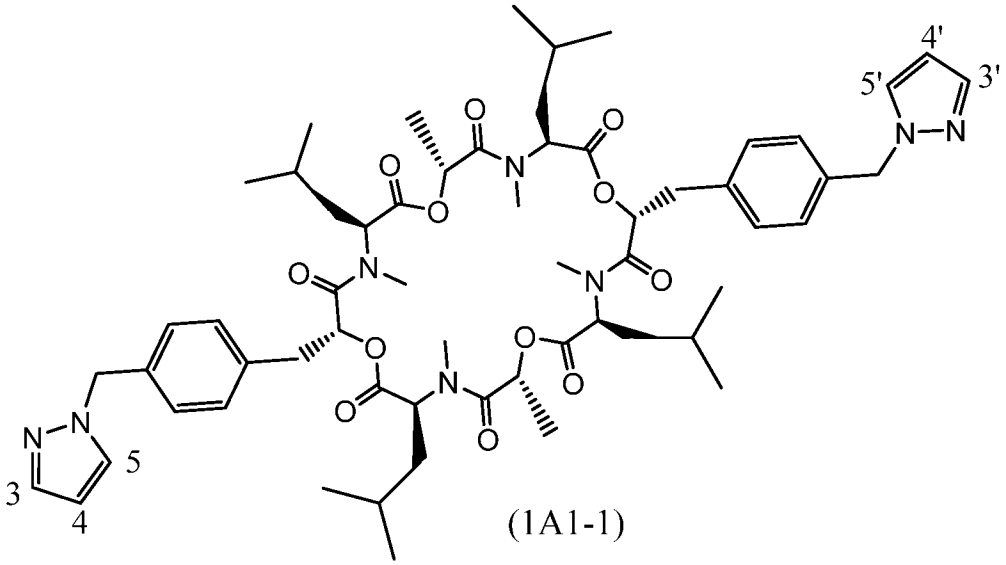


(1c-13)

To a stirred solution of intermediate (k, k') (40 mg, 0.04 mmol; Scheme 4) in THF (6mL) 3,5-bis-CF_3-pyrazole (47mg, 0.232mmol), TPP (60mg, 0.23mmol) were added at room temperature under argon atmosphere. Resulting mixture was cooled to 0°C and diethyl azodicarboxylate (DEAD; 36µL, 0.23mmol) was added. The mixture was warmed to room temperature and stirred for 48 hours. The volatiles were evaporated under reduced pressure and crude residue was dissolved in ethyl acetate (30mL). Organic layer was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude mass was purified by prep-HPLC to afford the compound (1c-13) (6mg, 11%) as a white solid. 2mg mono substituted product was also isolated after preparatory HPLC.

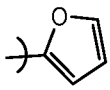
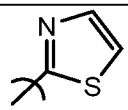
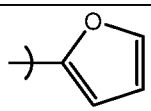
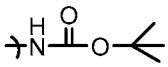
Mass data (ESI-MS m/z $[M+H]^+$) for the respective compounds is presented after each of the compound names in parentheses following the respective compound Tables. For example: Table 1a. (1a-1). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-bromo-3-cyano-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1264).

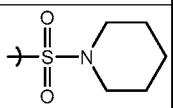
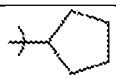
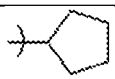
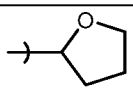
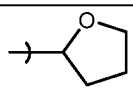
The following Formula (1A1-1) compounds (para/para) described in Tables 1a and 1b were prepared in accordance with the schemes and examples described herein.

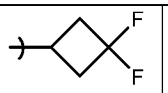
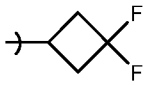
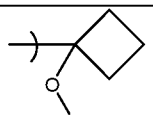
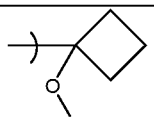
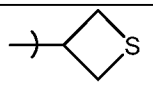
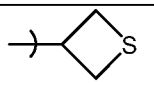
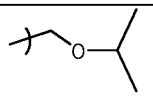
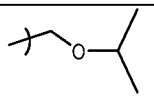
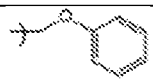
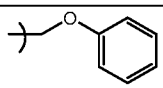


(1A1-1)

Table 1a. Formula (1A1-1) Compounds; Assymetric Pyrazole Substitutions

#	3	4	5	3'	4'	5'
1a-1	-CN	H	-CN	-CN	Br	H
1a-2	-CN	H	-CN	$-CH_2OH$	H	$-CH_2OH$
1a-3	-CN	H	-CN		H	$-CH_2OH$
1a-4		H			H	$-CH_2OH$
1a-5		H		phenyl	H	$-CH_2OH$
1a-6		H			H	$-CH_2OH$
1a-7	-CN	H	-CN	$-CHF_2$	H	
1a-8		H		methyl	$-CH_2OH$	H
1a-9	-CN	Br	H	H	Br	-CN
1a-10	-CN	H	-CN	$-CH_2OH$	H	
1a-11	H		H	-CN	H	-CN
1a-12	H	H	phenyl	-CN	H	-CN

1a-13		H		-CN	H	-CN
1a-14		H		$-CH_2OH$	H	
1a-15	H	phenyl	H	H	H	H
1a-16	H	Br	H	H	H	H
1a-17	H	H	H	H	t-butyl	H
1a-18	H	4-Cl-phenyl	H	H	H	H
1a-19	H	phenyl	H	H	methyl	H
1a-20	H	I	H	H	methyl	H
1a-21	H	I	H	H	H	H
1a-22	H	4-F-phenyl	H	H	methyl	H
1a-23	methyl		methyl	H	methyl	H
1a-24	H	Br	H	H	methyl	H
1a-25	methyl		methyl	H	methyl	H
1a-26	$-CF_3$	H	H	H	H	$-CF_3$
1a-27	H	4-Cl-phenyl	H	H	methyl	H
1a-28	phenyl	H	H	H	methyl	H
1a-29	$-CF_3$	H	H	H	methyl	H
1a-30	H	$-CF_3$	H	H	methyl	H
1a-31	Br	H	H	H	H	
1a-32	-CN	Br	H	H	$-NH_2$	H
1a-33	H	$-NHC(O)CF_3$	H	H	$-NH_2$	H
1a-34		H	H	H	H	
1a-35	isopropoxy	H	H	H	H	isopropoxy
1a-36	ethoxy	H	H	H	H	ethoxy
1a-37	$-CH_2OCH_3$	H	H	H	H	$-CH_2OCH_3$
1a-38	H	ethoxy	methyl	methyl	ethoxy	H
1a-39	H	isopropoxy	methyl	methyl	isopropoxy	H
1a-40	H	H			H	H

1a-41	H	H			H	H
1a-42	H	H			H	H
1a-43	H	H			H	H
1a-44	H	H			H	H
1a-45	H	H			H	H
1a-46	H	H	Cl	Cl	H	H

The following (1A1-1) compound names and example #'s refer to those compounds depicted in Table 1a. In one aspect of the invention, are Formula (1A1-1) compounds selected from the group consisting of:

(1a-1). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-bromo-3-cyano-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1264);

(1a-2). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((3,5-bis(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1220);

(1a-3). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((3-(furan-2-yl)-5-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1257);

(1a-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-(hydroxymethyl)-3-(thiazol-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1304);

(1a-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-(hydroxymethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1297);
(1a-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3-(furan-2-yl)-5-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1287);
(1a-7). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((5-cyclopropyl-3-(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1251);
(1a-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-(hydroxymethyl)-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1235);
(1a-9). 4-bromo-1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-bromo-5-cyano-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3-carbonitrile (1318);
(1a-10). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((5-cyclopropyl-3-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1231);
(1a-11). tert-butyl (1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((3,5-dicyano-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-4-yl)carbamate (1276);
(1a-12). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-14-(4-((5-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1236);

(1a-13). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1241);
(1a-14). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((5-cyclopropyl-3-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1261);
(1a-15). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1185);
(1a-16). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-bromo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1188);
(1a-17). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-(tert-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);
(1a-18). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-(4-chlorophenyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1220);
(1a-19). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1199);
(1a-20). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1249);
(1a-21). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-

4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1235);
(1a-22). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-(4-fluorophenyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1217);
(1a-23). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3,5-dimethyl-4-(pyrrolidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1285);
(1a-24). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-bromo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1202);
(1a-25). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3,5-dimethyl-4-(piperidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1299);
(1a-26). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((5-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1245);
(1a-27). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-(4-chlorophenyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1234);
(1a-28). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((3-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1199);
(1a-29). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1191);

(1a-30). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((4-methyl-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1191);
(1a-31). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3-bromo-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-bromo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1267);
(1a-32). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-amino-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-4-bromo-1H-pyrazole-3-carbonitrile (1228);
(1a-33). N-(1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-amino-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-4-yl)-2,2,2-trifluoroacetamide (1235);
(1a-34). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1246);
(1a-35). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(4-((3-isopropoxy-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-isopropoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1226);
(1a-36). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3-ethoxy-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-ethoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);
(1a-37). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(4-((3-(methoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-(methoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);

(1a-38). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[4-[(4-ethoxy-3-methyl-pyrazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(4-ethoxy-5-methyl-pyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1223);
(1a-39). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-[[4-[(4-isopropoxy-3-methyl-pyrazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(4-isopropoxy-5-methyl-pyrazol-1-yl)methyl]phenyl]methyl]-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1252);
(1a-40). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((3-(tetrahydrofuran-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((5-(tetrahydrofuran-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1248);
(1a-41). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3-(3,3-difluorocyclobutyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-(3,3-difluorocyclobutyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1288);
(1a-42). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(4-((3-(1-methoxycyclobutyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-(1-methoxycyclobutyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1276);
(1a-43). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((3-(thietan-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((5-(thietan-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1252);
(1a-44). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(4-((3-(isopropoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-(isopropoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1252);
(1a-45). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(4-((3-(phenoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((5-(phenoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1322); and

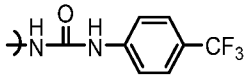
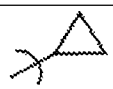
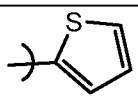
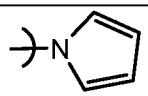
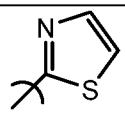
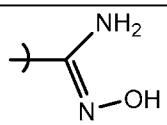
(1a-46). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3-chloro-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((5-chloro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1178).

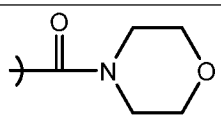
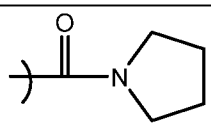
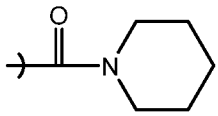
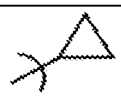
Table 1a'. Formula (1A1-1) Table 1a Compound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

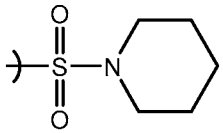
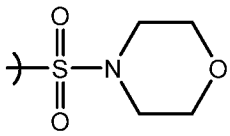
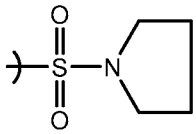
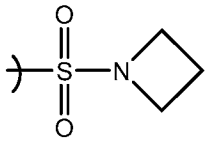
Example	NMR
1a-1	0.62 – 0.92 (m, 28 H), 1.11 – 1.69 (m, 14 H), 2.60 – 3.00 (m, 16 H), 4.34 (br d, 1 H), 4.74 - 5.82 (m, 11 H), 7.14 - 7.32 (m, 8 H), 7.92 (s, 1 H), 8.38 (s, 1 H)
1a-2	0.61 - 0.88 (m, 28 H), 1.13 - 1.63(m, 15 H), 2.61 – 3.04 (m, 15 H), 4.26 - 4.40 (m, 5 H), 4.96 (m, 13 H), 6.07 (s,1H), 7.01 (m,2 H), 7.18 (br t, 4H), 7.30 (m,2H), 7.92 (s,1H)
1a-5	0.67 - 0.94 (m, 28 H), 1.24 - 1.72 (m, 14 H), 2.63 - 3.13 (m, 16 H), 4.32 - 4.53 (m, 3 H), 4.90 - 5.74 (m, 12 H), 6.55 (s, 1 H), 6.57 (br s, 1 H), 6.63 (d, 1 H), 7.00 (d, 2 H), 7.24 (br d, 4 H), 7.37 (br d, 2 H), 7.76 (s, 1 H), 7.99 (s, 1 H)
1a-6	0.44 - 0.67 (m, 4 H), 0.67 - 0.95 (m, 30 H), 1.23 - 1.78 (m, 18 H), 2.68 - 3.02 (m, 15 H), 4.24 - 4.51 (m, 4 H), 5.02 - 5.72 (m, 14 H), 6.55 – 6.64 (m, 2 H), 7.01 - 7.05 (m, 4 H), 7.19 - 7.33 (m, 4 H), 7.76 (s, 1 H)
1a-8	0.43 - 0.65 (m, 4 H), 0.68 - 0.96 (m, 30 H), 1.18 - 1.33 (m, 6 H), 1.34 - 1.62 (m, 6 H), 1.66 - 1.79 (m, 3 H), 1.99 (s, 3 H), 2.68 (s, 2 H), 2.76 (br d, 4 H), 2.82 - 2.95 (m, 6 H), 3.03 (br s, 3 H), 3.84 (br s, 1 H), 4.16 (br s, 4 H), 4.34 (s, 3 H), 4.37 - 4.56 (m, 2 H), 4.63 (br s, 1 H), 5.00 - 5.72 (m, 9 H), 7.05 (br d, 2 H), 7.15 (br d, 2 H), 7.27 (br d, 4 H), 7.40 - 7.45 (m, 1 H)
1a-10	0.43 - 0.64 (m, 4 H), 0.67 - 0.94 (m, 30 H), 1.16 - 1.40 (m, 8 H), 1.40 - 1.61 (m, 4 H), 1.64 - 1.78 (m, 3 H), 2.64 - 2.79 (m, 6 H), 2.81 - 2.94 (m, 6 H), 2.97 - 3.11 (m, 3 H), 4.30 - 4.61 (m, 5 H), 4.91 - 5.84 (m, 10 H), 7.00 - 7.17 (m, 2 H), 7.19 - 7.27 (m, 4 H), 7.35 (br d, 2 H), 7.97 (s, 1 H)
1a-13	0.46 - 0.63 (m, 4 H), 0.68 - 0.95 (m, 30 H), 1.20 - 1.42 (m, 8 H), 1.42 - 1.63 (m, 4 H), 1.65 - 1.78 (m, 3 H), 2.65 - 2.79 (m, 6 H), 2.82 - 2.96 (m, 6 H), 2.99 - 3.12 (m, 3 H), 4.41 (br d, 1 H), 5.02 - 5.16 - 5.27 (m, 7 H), 5.34 (q, 2 H), 5.40 - 5.61 (m, 3 H), 5.62 - 5.73 (m, 4 H), 7.02 - 7.10 (m, 2 H), 7.21 - 7.29 (m, 4 H), 7.36 (br d, 2 H), 7.98 (s, 1 H)
1a-14	0.45 - 0.65 (m, 6 H), 0.68 - 0.95 (m, 32 H), 1.18 - 1.32 (m, 6 H), 1.33 - 1.49 (m, 3 H), 1.49 - 1.63 (m, 3 H), 1.65 - 1.82 (m, 4 H), 2.67 (s, 2 H), 2.76 (br d, 4 H), 2.81 - 2.94 (m, 6 H), 3.02 (br s, 2 H), 3.32 (s, 6 H), 4.30 - 4.36 (m, 2 H), 4.36 - 4.47 (m, 1 H), 5.00 - 5.25 (m, 8 H), 5.26 - 5.52 (m, 2 H), 5.56 - 5.71 (m, 2 H), 5.83 - 5.89 (m, 1 H), 7.04 (br d, 4 H), 7.25 (br s, 4 H)
1a-15	0.65-0.95 (m, 26H), 1.18-1.77 (m, 16H), 2.67-3.06 (m, 16 H), 4.39-5.70 (m, 12 H), 6.24-6.26 (m, 1 H), 7.13-7.35 (m, 11 H), 7.45 (s, 1 H), 7.54 (d, 2H), 7.77-7.79 (m, 1 H), 7.90-7.92 (m, 1 H), 8.23 (d, 1 H)
1a-16	0.67-0.96 (m, 26H), 1.18-1.76 (m, 16H), 2.67-3.06 (m, 16 H), 4.38-5.70 (m, 12 H), 6.25-6.27 (m, 1 H), 7.13-7.29 (m, 8 H), 7.44 (s, 1 H), 7.54-7.56 (m, 1 H), 7.75-7.77 (m, 1 H), 8.03-8.05 (m, 1 H)
1a-17	0.66-0.95 (m, 26H), 1.18 (s, 9 H) 1.19-1.75 (m, 16H), 2.67-3.06 (m, 16 H), 4.39-5.70 (m, 12 H), 6.25-6.26 (m, 1 H), 7.14-7.28 (m, 8 H), 7.34 (s, 1 H), 7.44 (s, 1 H), 7.54-7.56 (m, 1 H), 7.75-7.77 (m, 1 H)
1a-18	0.67-0.95 (m, 26H), 1.18-1.76 (m, 16H), 2.66-3.06 (m, 16 H), 4.39-5.71 (m, 12 H), 6.24-6.26 (m, 1 H), 7.14 (d, 2 H), 7.22-7.32 (m, 6 H), 7.39 (d, 2 H), 7.42-7.44 (m, 1 H), 7.57-7.60 (m, 2 H), 7.77-7.79 (m, 1 H), 7.92-7.94 (m, 1 H), 8.28-8.30 (m, 1 H)
1a-19	0.65-0.94 (m, 26H), 1.15-1.74 (m, 16H), 1.98 (s, 3 H), 2.66-3.08 (m, 16 H), 4.38-5.71 (m, 12H), 7.12-7.37 (m,12H), 7.48-7.50 (m,1H), 7.54 (d,2H), 7.89 (s,1H), 8.22 (d, 1 H)
1a-20	0.66-0.94 (m, 26H), 1.18-1.73 (m, 16H), 1.98 (s, 3 H), 2.67-3.07 (m, 16 H), 4.39-5.71 (m, 12 H), 7.12-7.29 (m, 9 H), 7.48-7.52 (m, 2 H), 7.95-7.97 (m, 1 H)

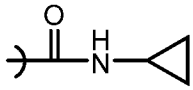
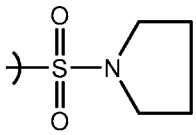
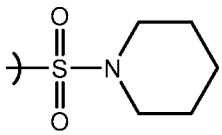
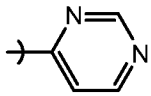
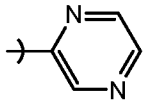
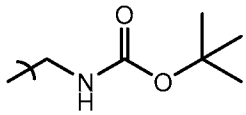
1a-21	0.66-0.94 (m, 26H), 1.17-1.74 (m, 16 H), 2.67-3.07 (m, 16 H), 4.39-5.72 (m, 12 H), 6.25 (s,1H), 7.13-7.29 (m, 8H), 7.44 (s,1H), 7.52 (s,1H), 7.76 (s,1H), 7.95-7.97 (m,1H)
1a-22	0.67-0.94 (m, 26H), 1.17-1.76 (m, 20 H), 1.98 (s, 3 H), 2.66-3.08 (m, 16 H), 4.39-5.71 (m, 12 H), 7.12-7.30 (m, 12 H), 7.48 (s, 1 H), 7.56-7.60 (m, 1 H), 7.87 (s, 1 H), 8.20-8.22 (m, 1 H)
1a-23	0.67-0.94 (m, 26H), 1.17-1.74 (m, 20H), 1.98 (s, 3 H), 2.29 (s, 3 H), 2.39 (s, 3 H), 2.67-3.08 (m, 20 H), 4.39-5.71 (m, 12 H), 7.06 (d, 2 H), 7.13 (d, 2 H), 7.23-7.31 (m, 5 H), 7.48-7.50 (m, 1 H)
1a-24	0.67-0.94 (m, 26H), 1.17-1.73 (m, 16H), 1.98 (s, 3 H), 2.67-3.08 (m, 16 H), 4.39-5.71 (m, 12 H), 7.12-7.30 (m, 9 H), 7.48-7.52 (m, 2 H), 8.02-8.04 (m, 1 H)
1a-25	0.67-0.94 (m, 26H), 1.17-1.76 (m, 22 H), 1.98 (s, 3 H), 2.27 (s, 3 H), 2.36 (s, 3 H), 2.67-3.06 (m, 20 H), 4.39-5.71 (m, 12 H), 7.06 (d, 2 H), 7.13 (d, 2 H), 7.23-7.30 (m, 5 H), 7.48-7.50 (m, 1 H)
1a-26	0.65-0.93 (m, 26H), 1.17-1.76 (m, 16 H), 2.67-3.08 (m, 16 H), 4.39-5.73 (m, 12 H), 6.72 (s, 1 H), 6.94 (s, 1 H), 7.05 (d,2H), 7.22-7.32 (m, 6 H), 7.73 (s, 1 H), 8.06 (s, 1 H)
1a-27	0.67-0.94 (m, 26H), 1.18-1.75 (m, 16 H), 1.98 (s, 3 H), 2.66-3.06 (m, 16 H), 4.39-5.70 (m, 12 H), 7.12 (d, 2 H), 7.21-7.30 (m, 7 H), 7.48 (br s, 1 H), 7.58 (d, 2 H), 7.91 (s, 1 H), 8.26-8.28 (m, 1 H)
1a-28	0.67-0.94 (m, 26H), 1.18-1.74 (m, 16 H), 1.98 (s, 3 H), 2.65-3.07 (m, 16 H), 4.39-5.70 (m, 12 H), 6.72 (s, 1 H), 7.13 (d, 2 H), 7.21-7.30 (m, 7 H), 7.35-7.48 (m, 4 H), 7.77 (d, 2 H), 7.84 (s, 1 H)
1a-29	0.67-0.94 (m, 26H), 1.18-1.76 (m, 16 H), 1.98 (s, 3 H), 2.67-3.08 (m, 16 H), 4.39-5.73 (m, 12 H), 7.13 (d, 2 H), 7.21-7.32 (m, 7 H), 7.48 (br s, 1 H), 7.88 (s, 1 H), 8.46-8.48 (m, 1 H)
1a-30	0.67-0.94 (m, 26H), 1.18-1.76 (m, 16 H), 1.98 (s, 3 H), 2.67-3.08 (m, 16 H), 4.39-5.73 (m, 12 H), 6.72 (s, 1 H), 7.13 (d, 2H), 7.21-7.32 (m, 7 H), 7.48 (br s, 1 H), 8.06 (s, 1 H)
1a-31	0.67 - 0.95 (m, 27 H) 1.17 - 1.31 (m, 7 H) 1.34 (br s, 2 H) 1.43 (br s, 2 H) 1.47 - 1.74 (m, 6 H) 2.64 - 2.80 (m, 6 H) 2.80 - 2.95 (m, 7 H) 3.03 (br s, 3 H) 4.41 (br d, *J* = 7.70 Hz, 1 H) 4.99 - 5.16 (m, 3 H) 5.18 - 5.37 (m, 6 H) 5.38 - 5.46 (m, 1 H) 5.47 - 5.57 (m, 1 H) 5.63 - 5.73 (m, 1 H) 6.38 (s, 1 H) 6.49 (s, 1 H) 7.06 (br d, *J* = 7.58 Hz, 2 H) 7.19 (br d, *J* = 7.70 Hz, 2 H) 7.29 (br s, 4 H) 7.58 (s, 1 H) 7.84 (s, 1 H)
1a-32	0.74 – 0.87 (m, 28 H), 1.27 – 1.71 (m, 15 H), 2.68 – 3.04 (m, 16 H), 5.04 – 5.76 (m, 12 H), 7.16 (m, 3 H), 7.27 (m, 6H), 7.64 (br s, 1 H), 9.13 (br s, 2 H)
1a-34	0.67 - 0.94 (m, 26 H), 1.24 - 1.90 (m, 30 H), 2.66 - 3.01 (m, 18 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.70 (m, 13 H), 6.05 (s, 1 H), 6.10 (s, 1 H), 6.98 - 7.60 (m, 10 H)
1a-35	0.69 - 0.94 (m, 25 H), 1.20 - 1.69 (m, 29 H), 2.67 - 3.02 (m, 16 H), 4.42 - 4.59 (m, 3 H), 5.02 - 5.68 (m, 11 H), 7.05 - 7.25 (m, 11 H), 7.54 (bs, 1 H)
1a-36	0.61 - 0.99 (m, 27 H), 1.15 - 1.77 (m, 21 H), 2.64 - 2.95 (m, 13 H), 2.96 – 3.11 (m, 3 H), 3.98 - 4.15 (m, 4 H), 4.37 - 4.46 (m, 1 H), 4.97 - 5.74 (m, 13 H), 7.05 (br d, 2 H), 7.12 (br d, 2 H), 7.20 – 7.32 (m, 5 H), 7.56 (m, 1 H)
1a-37	0.68-0.94 (m, 26H), 1.18-1.75 (m, 16 H), 2.67-3.07 (m, 16 H), 3.20-3.22 (m ,6 H), 4.29 (s, 2 H), 4.38-5.71 (m, 14 H), 6.22 (s, 1 H), 6.28 (s, 1 H), 7.06 (d, 2 H), 7.15 (d, 2 H), 7.25-7.28 (m, 4 H), 7.42 (s, 1 H), 7.72 (s, 1 H).
1a-38	0.71 - 0.95 (m, 25 H), 1.23 - 1.34 (m, 12 H), 1.36 - 1.70 (m, 10 H), 2.00 (s, 6 H), 2.67 - 3.04 (m, 16 H), 3.38 - 3.91 (m, 4 H), 4.40 - 4.43 (m, 1 H), 5.06 - 5.72 (m, 12 H), 6.98 - 7.13 (m, 4 H), 7.25 - 7.41 (m, 6 H)
1a-39	0.70 - 0.96 (m, 26 H), 1.19 - 1.66 (m, 26 H), 1.98 (s, 6 H), 2.67 - 3.02 (m, 16 H), 4.01 - 4.32 (m, 4 H), 4.40 - 4.43 (m, 1 H), 5.06 - 5.35 (m, 11 H), 6.97 - 7.13 (m, 4 H), 7.18 - 7.43 (m, 6 H)

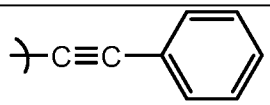
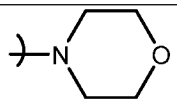
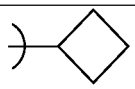
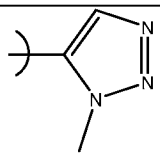
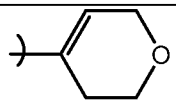
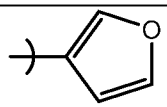
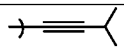
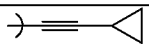
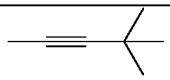
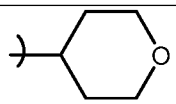
Table 1b. Formula (1A1-1) Compounds; Symmetric (bis) Pyrazole Substitutions

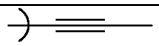
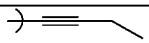
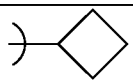
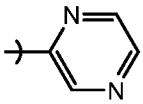
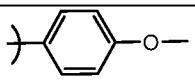
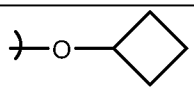
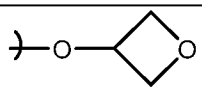
#	3 and 3’	4 and 4’	5 and 5’
1b-1	methyl	$-NH_2$	methyl
1b-2	-CN	Cl	H
1b-3	H	$-NHC(O)OCH_3$	H
1b-4	H		H
1b-5	H	$-NHC(O)NHC(CH_3)_3$	H
1b-6	H	$-NH_2$	H
1b-7	$-CH_2CN$	H	methyl
1b-8	$-CH_2OH$	H	
1b-9		H	H
1b-10	H	$-NHC(O)OC(CH_3)_3$	H
1b-11	H		H
1b-12	H	$-NHC(O)OCH_2CF_3$	H
1b-13	H		H
1b-14		H	
1b-15	$-CF_3$	H	$-CF_3$
1b-16	methyl	OH	methyl
1b-17	H	F	H
1b-18	H	-OH	H
1b-19	H	isopropoxy	H
1b-20	H	$-SCH_3$	H
1b-21	H	ethoxy	H
1b-22	H		H
1b-23	H	H	H

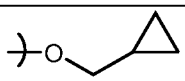
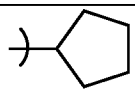
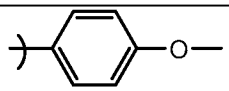
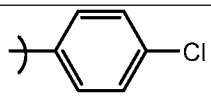
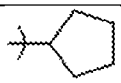
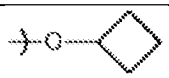
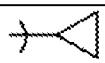
1b-24	H	methyl	H
1b-25	H	Br	H
1b-26	H	phenyl	H
1b-27	H	4-F-phenyl	H
1b-28	H	4-Cl-phenyl	H
1b-29	methyl	H	methyl
1b-30	H	t-butyl	H
1b-31	H	ethyl	H
1b-32	H	ethynyl	H
1b-33	H	pyridin-4-yl	H
1b-34	H	$-CF_3$	H
1b-35	H	Cl	H
1b-36	methyl	methyl	methyl
1b-37	H	isopropyl	H
1b-38	H	$-C(O)CH_3$	H
1b-39	H	$-C(O)OCH_2CH_3$	H
1b-40	H		H
1b-41	H		H
1b-42	H		H
1b-43	methyl	Br	H
1b-44	methyl	Br	methyl
1b-45	H		H
1b-46	H	I	H
1b-47	H	propyl	H
1b-48	methyl	ethyl	methyl

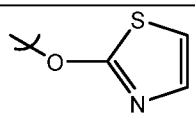
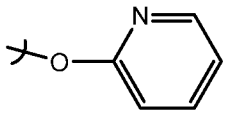
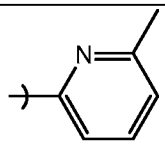
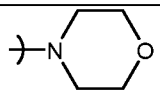
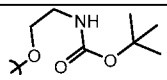
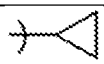
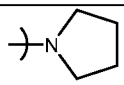
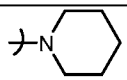
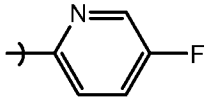
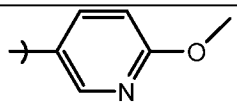
1b-49	H		H
1b-50	H		H
1b-51	methyl	Cl	methyl
1b-52	H	methoxy	H
1b-53	H	-C(O)NHCH$_3$	H
1b-54	H		H
1b-55	isopropyl	H	isopropyl
1b-56	H	-C(O)N(CH$_3$)$_2$	H
1b-57	methyl	propyl	methyl
1b-58	methyl	-NO$_2$	methyl
1b-59	H	-S(O)$_2$CH$_3$	H
1b-60	H	-SCH(CH$_3$)$_2$	H
1b-61	H		H
1b-62	H	-CHF$_2$	H
1b-63	Br	H	H
1b-64	I	H	H
1b-65	methyl	-CH$_2$CH$_2$OH	methyl
1b-66	-CN	H	-CN
1b-67		H	H
1b-68	phenyl	H	H
1b-69	-CF$_3$	H	H
1b-70	H	-NO$_2$	H
1b-71	H	pyridin-2yl	H
1b-72	H	-NHC(O)CH$_3$	H

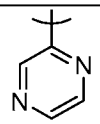
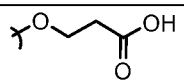
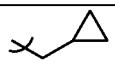
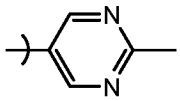
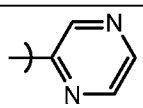
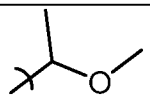
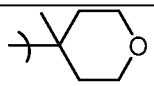
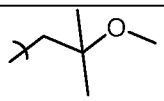
1b-73	H	4-methyl-pyridin-3yl	H
1b-74	H		H
1b-75	H	$-CH_2CH_2OH$	H
1b-76	H	$-NHS(O)_2CH_3$	H
1b-77	H	pyridin-3yl	H
1b-78	H	cyclopentyl	H
1b-79	isopropyl	H	H
1b-80	methyl		methyl
1b-81	t-butyl	H	H
1b-82		H	H
1b-83	$-CH_2OH$	H	$-CH_2OH$
1b-84	methyl	$-NHC(O)CH_3$	methyl
1b-85	methyl		methyl
1b-86	H		H
1b-87	H		H
1b-88	H	$-CH_2NHC(O)CH_3$	H
1b-89	$-CHF_2$	H	$-CHF_2$
1b-90	H	$-C(O)NH_2$	H
1b-91	H		H
1b-92	methyl	$-S(O)_2NH_2$	methyl
1b-93	-CN	Br	H
1b-94	methyl	H	H
1b-95	ethyl	H	H

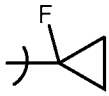
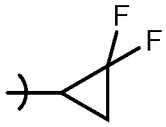
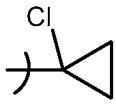
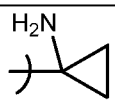
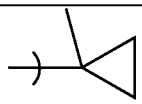
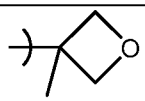
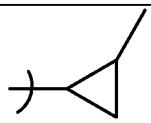
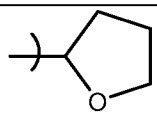
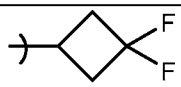
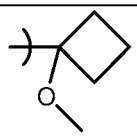
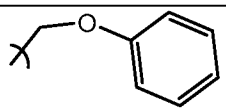
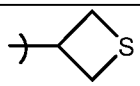
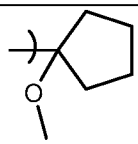
1b-96	Cl	H	H
1b-97	$-CH_2OH$	H	H
1b-98	$-CH_2NH_2$	H	H
1b-99	$-NHC(O)CH_3$	H	H
1b-100	$-C(O)OC(CH_3)_3$	H	H
1b-101	H	$-S(O)_2NH_2$	H
1b-102	H		H
1b-103	-CN	H	H
1b-104	ethoxy	H	H
1b-105		H	H
1b-106		H	H
1b-107	H		H
1b-108	H	H	
1b-109	H		H
1b-110	methyl	F	methyl
1b-111		H	H
1b-112	H		H
1b-113	H		H
1b-114	H		H
1b-115	methoxy	H	H
1b-116	H		H
1b-117	methyl	-CN	methyl

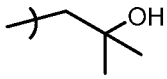
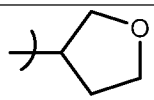
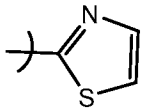
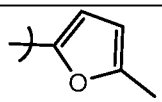
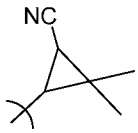
1b-118	H		H
1b-119	H		H
1b-120	pyridin-2yl	H	H
1b-121	$-NO_2$	H	H
1b-122		$-NO_2$	
1b-123	ethyl	$-NO_2$	ethyl
1b-124	$-CH_2OH$	methyl	$-CF_3$
1b-125	-CN	phenyl	H
1b-126	H	H	isopropyl
1b-127	H	H	t-butyl
1b-128	H	H	phenyl
1b-129	H	H	
1b-130	methyl	$-CF_3$	methyl
1b-131		H	H
1b-132	$-S(O)_2NH_2$	H	H
1b-133	ethyl	$-NH_2$	ethyl
1b-134		H	H
1b-135	methyl	-CN	H
1b-136	-CN	methyl	H
1b-137	No Example		
1b-138	pyridin-4yl	H	H
1b-139	pyridin-3yl	H	H
1b-140	H	$-OCHF_2$	H
1b-141	H		H
1b-142	H		H
1b-143	$-NH_2$	H	H
1b-144	H	H	$-NH_2$

1b-145		$-NH_2$	
1b-146	H		H
1b-147	No example		
1b-148		H	H
1b-149	H	H	
1b-150	H	$-OCH_2CF_3$	H
1b-151	isopropoxy	H	H
1b-152	H	methyl	methyl
1b-153	H	H	
1b-154	H	H	
1b-155	H	$-CH_2OCH_3$	H
1b-156	$-OCHF_2$	H	H
1b-157	H	$-CH_2OCH_2CH_3$	H
1b-158	methyl	$-CH_2OH$	H
1b-159	ethoxy	H	methyl
1b-160	H	H	methyl
1b-161		H	H
1b-162	$-CF_3$	$-CH_2OH$	H
1b-163	methyl	H	ethoxy
1b-164	isopropoxy	H	methyl
1b-165	H	H	ethyl
1b-166	H	H	$-CH_2OCH_3$
1b-167	H	isopropoxy	H
1b-168	methoxy	H	methyl
1b-169	ethyl	H	ethoxy
1b-170		H	ethoxy

1b-171	H	ethoxy	H
1b-172	H	isobutoxy	H
1b-173	H	H	pyridin-2yl
1b-174	H		H
1b-175	H		H
1b-176	H	H	$-CH_2OCH_2CH_3$
1b-177	H	H	
1b-178	phenyl	H	ethoxy
1b-179	H		H
1b-180	H		H
1b-181	methyl	H	
1b-182	H		H
1b-183	H		H
1b-184	H	$-CH_2OCH(CH_3)_2$	H
1b-185	H	$-OCH_2CH_2NH_2$	H
1b-186	ethyl	H	methyl
1b-187	methyl	H	ethyl
1b-188	methyl	isopropoxy	methyl
1b-189	H	H	
1b-190	H	H	
1b-191	methyl	ethoxy	methyl

1b-192	H	$-N(CH_3)_2$	H
1b-193	H	$-N(CH_2CH_3)_2$	H
1b-194	-CN	H	methyl
1b-195		H	H
1b-196	$-S(O)_2NH_2$	H	H
1b-197	H	ethoxy	methyl
1b-198	methyl	ethoxy	H
1b-199	methyl	Isopropoxy	H
1b-200	No example		
1b-201	H	$-OCH_2OCH_3$	H
1b-202	H		H
1b-203	H	$-OCH_2CH_2OCH_3$	H
1b-204	No example		
1b-205	H	H	propyl
1b-206	H	H	
1b-207	H	H	
1b-208	H	H	
1b-209	H	H	isobutyl
1b-210	H	H	sec-butyl
1b-211	H	H	$-CHF_2$
1b-212	H	H	
1b-213	H	H	
1b-214	H	H	

1b-215	H	H	
1b-216	H	H	
1b-217	H	H	
1b-218	H	H	
1b-219	H	H	
1b-220	H	H	$-C(CH_3)_2OCH_3$
1b-221	H	H	
1b-222	H	H	
1b-223	H	H	
1b-224	H	H	
1b-225	H	H	
1b-226	H	H	
1b-227	H	H	
1b-228	H	H	$-CH_2OCH(CH_3)_2$
1b-229	H	H	

1b-230	H	H	
1b-231	H	H	
1b-232	H	H	
1b-233	H	H	
1b-234	H	H	
1b-235	H	H	

The following Formula (1A1-1) compound names and example #'s refer to those compounds depicted in Table 1b. In one aspect of the invention, are Formula (1A1-1) compounds selected from the group consisting of:

(1b-1). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-amino-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);

(1b-2). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(4-chloro-1H-pyrazole-3-carbonitrile) (1229);

(1b-3). dimethyl ((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))dicarbamate (1256);

(1b-4). 1,1'-((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-

phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))bis(3-(4-(trifluoromethyl)-phenyl)urea) (1215);

(1b-5). 1,1'-((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))bis(3-(tert-butyl)urea) (1339);

(1b-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-amino-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1140);

(1b-7). 2,2'-((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(5-methyl-1H-pyrazole-1,3-diyl))diacetonitrile (1216);

(1b-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopropyl-3-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);

(1b-9). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(thiophen-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1275);

(1b-10). di-tert-butyl ((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))dicarbamate (1241);

(1b-11). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(1H-pyrrol-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1240);

(1b-12). bis(2,2,2-trifluoroethyl) ((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))dicarbamate (1392);

(1b-13). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(thiazol-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1276);
(1b-14). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis({4-[(3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl]phenyl}methyl)-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1268);
(1b-15). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[(4-{[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1381);
(1b-16). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis({4-[(4-hydroxy-3,5-dimethyl-1H-pyrazol-1-yl)methyl]phenyl}methyl)-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1196);
(1b-17). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1145);
(1b-18). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-hydroxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1141);
(1b-19). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis[[4-[(4-isopropoxypyrazol-1-yl)methyl]phenyl]methyl]-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1225);
(1b-20). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-[(4-methylsulfanylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1201);
(1b-21). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-ethoxypyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1199);

(1b-22). N'-hydroxy-1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[[4-[(Z)-N'-hydroxycarbamimidoyl]pyrazol-1-yl]methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrazole-4-carboxamidine (1227);

(1b-23). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-(pyrazol-1-ylmethyl)phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1110);

(1b-24). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-[(4-methylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1148);

(1b-25). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-bromopyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1268).

(1b-26). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-[(4-phenylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1262);

(1b-27). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[[4-(4-fluorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1298);

(1b-28). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[[4-(4-chlorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1332);

(1b-29). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(3,5-dimethylpyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1166);

(1b-30). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-tert-butylpyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1222);

(1b-31). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-ethylpyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1166);
(1b-32). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis({4-[(4-ethynyl-1H-pyrazol-1 yl)methyl]phenyl}methyl)-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1156);
(1b-33). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyridin-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);
(1b-34). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone(1245);
(1b-35). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-chloro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1178);
(1b-36). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3,4,5-trimethyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(1b-37). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(1b-38). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-acetyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1193);
(1b-39). diethyl 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-4-carboxylate) (1253);
(1b-40). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(morpholine-4-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1336);

(1b-41). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyrrolidine-1-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1304);

(1b-42). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(piperidine-1-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1332);

(1b-43). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-bromo-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1295);

(1b-44). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1323);

(1b-45). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1189);

(1b-46). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1361);

(1b-47). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);

(1b-48). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-ethyl-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1222);

(1b-49). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(piperidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1404);

(1b-50). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(morpholinosulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1408);

(1b-51). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1234);

(1b-52). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-methoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1169);

(1b-53). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(N-methyl-1H-pyrazole-4-carboxamide) (1223);

(1b-54). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyrrolidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1376);

(1b-55). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-diisopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1278);

(1b-56). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(N,N-dimethyl-1H-pyrazole-4-carboxamide) (1252);

(1b-57). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-dimethyl-4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);

(1b-58). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-dimethyl-4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1255);

(1b-59). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(methylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1266);

(1b-60). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-(isopropylthio)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1258);

(1b-61). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(azetidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1348);

(1b-62). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1209);

(1b-63). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-bromo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1267);

(1b-64). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1361);

(1b-65). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-66). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-3,5-dicarbonitrile) (1209);

(1b-67). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1189);
(1b-68). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1262);
(1b-69). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1245);
(1b-70). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1199);
(1b-71). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);
(1b-72). N,N'-((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))diacetamide (1223);
(1b-73). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(6-methylpyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1292);
(1b-74). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(N-cyclopropyl-1H-pyrazole-4-carboxamide) (1276);
(1b-75). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(2-hydroxyethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);
(1b-76). N,N'-((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-

4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))dimethanesulfonamide (1296);
(1b-77). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);
(1b-78). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1246);
(1b-79). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((3-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(1b-80). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-dimethyl-4-(pyrrolidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1432);
(1b-81). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-(tert-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1222);
(1b-82). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(thiophen-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1274);
(1b-83). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-bis(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1229);
(1b-84). N,N'-((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(3,5-dimethyl-1H-pyrazole-1,4-diyl))diacetamide (1280);
(1b-85). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-dimethyl-4-(piperidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-

hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1460);

(1b-86). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyrimidin-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1266);

(1b-87). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyrazin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1266);

(1b-88). N,N'-(((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))bis(methylene))diacetamide (1252);

(1b-89). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1309);

(1b-90). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-4-carboxamide) (1195);

(1b-91). di-tert-butyl (((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))bis(methylene))dicarbamate (1368);

(1b-92). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((3,5-dimethyl-4-sulfamoyl-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (1324);

(1b-93). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-

4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(4-bromo-1H-pyrazole-3-carbonitrile) (1317);
(1b-94). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1137);
(1b-95). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-ethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);
(1b-96). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-chloro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1178);
(1b-97). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1169);
(1b-98). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1167);
(1b-99). N,N'-((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,3-diyl))diacetamide (1223);
(1b-100). di-tert-butyl 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-3-carboxylate) (1310);
(1b-101). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-14-(4-((4-sulfamoyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-sulfonamide (1268);
(1b-102). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(phenylethynyl)-1H-pyrazol-1-

yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1310);

(1b-103). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-3-carbonitrile) (1159);

(1b-104). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-ethoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);

(1b-105). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-morpholino-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1280);

(1b-106). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-cyclobutyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1218);

(1b-107). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1272);

(1b-108). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1189);

(1b-109). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(3,6-dihydro-2H-pyran-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1274);

(1b-110). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-fluoro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1201);

(1b-111). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-(furan-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1241);

(1b-112). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(3-methylbut-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1242);

(1b-113). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(cyclopropylethynyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1238);

(1b-114). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(3,3-dimethylbut-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1270);

(1b-115). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((3-methoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1169);

(1b-116). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1278);

(1b-117). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(3,5-dimethyl-1H-pyrazole-4-carbonitrile) (1215);

(1b-118). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(prop-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1185);

(1b-119). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(but-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1214);

(1b-120). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(pyridin-2-yl)-1H-pyrazol-1-

yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);

(1b-121). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-nitro-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1199);

(1b-122). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-dicyclopropyl-4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1360);

(1b-123). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-diethyl-4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1312);

(1b-124). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-(hydroxymethyl)-4-methyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1333);

(1b-125). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(4-phenyl-1H-pyrazole-3-carbonitrile) (1312);

(1b-126). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194)

(1b-127). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(tert-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1222);

(1b-128). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1262);

(1b-129). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclobutyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1218);
(1b-130). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-dimethyl-4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1301);
(1b-131). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(pyrazin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1265);
(1b-132). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-14-(4-((3-sulfamoyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3-sulfonamide (1267);
(1b-133). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-amino-3,5-diethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1252);
(1b-134). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((3-(4-methoxyphenyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1322);
(1b-135). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(3-methyl-1H-pyrazole-4-carbonitrile) (1187);
(1b-136). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(4-methyl-1H-pyrazole-3-carbonitrile) (1187);
(1b-137). No Example;
(1b-138). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(pyridin-4-yl)-1H-pyrazol-1-

yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);

(1b-139). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);

(1b-140). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(difluoromethoxy)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1241);

(1b-141). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-cyclobutoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);

(1b-142). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(oxetan-3-yloxy)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-143). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-amino-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1139);

(1b-144). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-amino-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1139);

(1b-145). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-amino-3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1300);

(1b-146). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(cyclopropylmethoxy)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);

(1b-147). No example;

(1b-148). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1246);
(1b-149). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-(4-methoxyphenyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1322);
(1b-150). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(2,2,2-trifluoroethoxy)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1305);
(1b-151). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((3-isopropoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1226);
(1b-152). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);
(1b-153). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(4-chlorophenyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1330);
(1b-154). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1246);
(1b-155). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-(methoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);
(1b-156). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-(difluoromethoxy)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1241);
(1b-157). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(ethoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1226);

(1b-158). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(hydroxymethyl)-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);

(1b-159). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-ethoxy-5-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1226);

(1b-160). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-methyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1137);

(1b-161). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-cyclobutoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);

(1b-162). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(hydroxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1305);

(1b-163). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethoxy-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1226);

(1b-164). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((3-isopropoxy-5-methyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-165). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);

(1b-166). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-(methoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);

(1b-167). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-isopropoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,24-pentamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1212);

(1b-168). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((3-methoxy-5-methyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);

(1b-169). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethoxy-3-ethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-170). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-cyclopropyl-5-ethoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1278);

(1b-171). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(2-(4-ethoxy-1H-pyrazol-1-yl)propan-2-yl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-172). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-isobutoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-173). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);

(1b-174). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(thiazol-2-yloxy)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1308);

(1b-175). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyridin-2-yloxy)-1H-pyrazol-1-

yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1296);

(1b-176). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(ethoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1226);

(1b-177). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(6-methylpyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1292);

(1b-178). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethoxy-3-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1350);

(1b-179). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-morpholino-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1280);

(1b-180). di-tert-butyl ((((((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrazole-1,4-diyl))bis(oxy))bis(ethane-2,1-diyl))dicarbamate (1428);

(1b-181). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopropyl-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1218);

(1b-182). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(pyrrolidin-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1248);

(1b-183). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(piperidin-1-yl)-1H-pyrazol-1-

yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1276);

(1b-184). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-(isopropoxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-185). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(2-aminoethoxy)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1228);

(1b-186). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((5-ethyl-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3-ethyl-5-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);

(1b-187). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethyl-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);

(1b-188). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-isopropoxy-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1282);

(1b-189). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(5-fluoropyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1300);

(1b-190). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-(6-methoxypyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1324);

(1b-191). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-ethoxy-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-192). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(dimethylamino)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1196);

(1b-193). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(diethylamino)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1252);

(1b-194). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(5-methyl-1H-pyrazole-3-carbonitrile) (1187)

(1b-195). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-[(3-pyrazin-2-ylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1264);

(1b-196). 1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-14-[[4-[(3-sulfamoylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrazole-3-sulfonamide (1265);

(1b-197). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-ethoxy-5-methyl-pyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1224);

(1b-198). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-ethoxy-3-methyl-pyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1224);

(1b-199). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis[[4-[(4-isopropoxy-3-methyl-pyrazol-1-yl)methyl]phenyl]methyl]-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1252);

(1b-200). No example;

(1b-201). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis[[4-[[4-(methoxymethoxy)pyrazol-1-yl]methyl]phenyl]methyl]-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1228);

(1b-202). 3-[1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[[4-(2-carboxyethoxy)pyrazol-1-yl]methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrazol-4-yl]oxypropanoic acid (1284);

(1b-203). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis[[4-[[4-(2-methoxyethoxy)pyrazol-1-yl]methyl]phenyl]methyl]-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1256);

(1b-204). No example;

(1b-205). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-propyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1193);

(1b-206). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(cyclopropylmethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1217);

(1b-207). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(2-methylpyrimidin-5-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1293);

(1b-208). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(pyrazin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1265);

(1b-209). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-isobutyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1221);

(1b-210). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(sec-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1221);
(1b-211). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1209);
(1b-212). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-(1-methoxyethyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1225);
(1b-213). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(4-methyltetrahydro-2H-pyran-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1305);
(1b-214). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-(2-methoxy-2-methylpropyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1281);
(1b-215). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(1-fluorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1225);
(1b-216). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(2,2-difluorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1261);
(1b-217). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(1-chlorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1258);
(1b-218). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(1-aminocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1220);

(1b-219). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(1-methylcyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1218);

(1b-220). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-(2-methoxypropan-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);

(1b-221). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(3-methyloxetan-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);

(1b-222). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(2-methylcyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1218);

(1b-223). (3S,6R,12R,15S,18R,21S,24R)-4,6,10,16,18,22-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-12,24-bis[(4-{[5-(oxolan-2-yl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1248);

(1b-224). (3S,6R,9S,12R,18R,21S,24R)-6,18-bis[(4-{[5-(3,3-difluorocyclobutyl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-ocatone (1288);

(1b-225). (3S,6R,9S,12R,18R,21S,24R)-6,18-bis[(4-{[5-(1-methoxycyclobutyl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-ocatone (1276);

(1b-226). (3S,6R,12R,15S,18R,21S,24R)-4,6,10,16,18,22-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-12,24-bis[(4-{[5-(phenoxymethyl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1320);

(1b-227). (3S,6R,12R,15S,18R,21S,24R)-4,6,10,16,18,22-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-12,24-bis[(4-{[5-(thietan-3-yl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-ocatone (1252);

(1b-228). (3S,6R,12R,15S,18R,21S,24R)-4,6,10,16,18,22-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-12,24-bis({[4-({5-[(propan-2-yloxy)methyl]-1H-pyrazol-1-yl}methyl)phenyl]methyl})-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1252);

(1b-229). (3S,6R,9S,12R,18R,21S,24R)-6,18-bis[(4-{[5-(1-methoxycyclopentyl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1304);

(1b-230). (3S,6R,9S,12R,18R,21S,24R)-6,18-bis[(4-{[5-(2-hydroxy-2-methylpropyl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-ocatone (1251);

(1b-231). (3S,6R,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(tetrahydrofuran-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1249);

(1b-232). (3S,6R,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(thiazol-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1275);

(1b-233). (3S,6R,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(5-methylfuran-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1269);

(1b-234). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(2,2-dimethylcyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1246); and

(1b-235). (1S,3S)-3-(1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((5-((1R,3R)-3-cyano-2,2-dimethylcyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-

tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-5-yl)-2,2-dimethylcyclopropane-1-carbonitrile (1296).

Table 1b'. Formula (1A1-1) Table 1b Compound NMR's (1H NMR (400MHz, DMSO-d_6) δ ppm)

Example	NMR
1b-3	0.67 - 0.82 (m, 18 H), 0.82 - 0.96 (m, 9 H), 1.16 - 1.38 (m, 8 H), 1.40 - 1.62 (m, 5 H), 1.65 - 1.74 (m, 2 H), 2.67 (s, 2 H), 2.72 (s, 2 H), 2.77 (s, 2 H), 2.81 - 2.94 (m, 7 H), 2.98 - 3.09 (m, 3 H), 3.32 (s, 9 H), 3.60 (s, 6 H), 4.41 (br d, 1 H), 5.00 - 5.17 (m, 3 H), 5.21 (s, 5 H), 5.26 - 5.53 (m, 2 H), 5.64 - 5.72 (m, 1 H), 7.15 (br d, 4 H), 7.23 - 7.34 (m, 6 H), 7.67 (br s, 2 H), 9.38 (s, 2 H)
1b-4	0.68 - 0.82 (m, 18 H), 0.82 - 0.96 (m, 10 H), 1.22 (br d, 6 H), 1.25 - 1.37 (m, 3 H), 1.38 - 1.76 (m, 8 H), 2.67 (s, 4 H), 2.70 - 2.96 (m, 9 H), 2.99 - 3.10 (m, 3 H), 4.38 - 4.48 (m, 1 H), 5.00 - 5.07 (m, 1 H), 5.10 (br d, 2 H), 5.14 - 5.29 (m, 4 H), 5.36 (q, 1 H), 5.48 - 5.59 (m, 1 H), 5.64 - 5.74 (m, 1 H), 7.19 (br d, 4 H), 7.29 (br d, 4 H), 7.42 (s, 2 H), 7.55 - 7.67 (m, 6 H), 7.80 (d, 2 H), 8.83 (br s, 2 H), 9.31 (br s, 2 H)
1b-6	0.67 - 0.97 (m, 30 H), 1.17 - 1.39 (m, 10 H), 1.42 (s, 3 H), 1.46 - 1.74 (m, 7 H), 2.69 (br d, 4 H), 2.75 - 2.95 (m, 9 H), 2.98 - 3.11 (m, 3 H), 5.02 - 5.25 (m, 2 H), 5.29 - 5.56 (m, 2 H), 5.64 - 5.76 (m, 2 H), 7.16 (br d, 4 H), 7.22 - 7.34 (m, 6 H), 7.64 (br s, 2 H), 9.13 (br s, 2 H)
1b-14	0.41 - 0.61 (m, 8 H), 0.70 - 0.94 (m, 32 H), 1.24 - 1.75 (m, 19 H), 2.67 - 3.01 (m, 16 H), 4.39 - 4.44 (m, 1 H), 5.01 - 5.68 (m, 14 H), 7.03 - 7.05 (m, 5 H), 7.23 - 7.25 (m, 5 H)
1b-15	0.77 - 0.92 (m, 26 H), 1.27 - 1.72 (m, 16 H), 2.66 - 3.05 (m, 16 H), 4.39 - 4.41 (m, 1 H), 5.01 - 5.69 (m, 11 H), 7.11 - 7.13 (m, 4 H), 7.32 - 7.33 (m, 4 H), 7.63 (s, 2 H)
1b-16	0.80 - 0.95 (m, 26 H), 1.28 - 1.70 (m, 16 H), 1.96 - 2.01 (m, 12 H), 2.67 - 3.01 (m, 16 H), 4.39 - 4.42 (m, 1 H), 5.05 - 5.68 (m, 11 H), 6.95 -6.97 (m, 4 H), 7.24 - 7.25 (m, 4 H), 7.52 (br s, 2 H)
1b-17	0.65 - 0.94 (m, 24 H), 1.23 - 1.73 (m, 17 H), 2.67 - 3.03 (m, 16 H), 4.37 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 12 H), 7.16 - 7.18 (m, 4 H), 7.27 - 7.29 (m, 4 H), 7.46 (s, 2 H), 7.91 (s, 2 H)
1b-18	0.67 - 0.95 (m, 24 H), 1.19 - 1.70 (m, 17 H), 2.68 - 3.02 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.02 - 5.70 (m, 12 H), 6.99 (s, 2 H), 7.10 - 7.12 (m, 4 H), 7.18 - 7.27 (m, 6 H), 8.39 (s, 2 H)
1b-19	0.59 - 1.04 (m, 26 H), 1.08 - 1.84 (m, 28 H), 2.60 - 3.18 (m, 16 H), 3.99 - 4.21 (m, 2 H), 4.38 - 4.47 (m, 1 H), 4.97 - 5.82 (m, 11 H), 6.95 - 7.68 (m, 12 H)
1b-20	0.67 - 0.95 (m, 26 H), 1.17 - 1.76 (m, 16 H,) 2.28 (s, 6 H), 2.65 - 2.95 (m, 13 H,) 3.00 - 3.11 (m, 3 H), 4.35 - 4.47 (m, 1 H), 4.96 - 5.57 (m, 10 H), 5.63 - 5.75 (m, 1 H), 7.18 (m, 4 H), 7.25 - 7.33 (m, 4 H), 7.45 - 7.52 (m, 2 H), 7.83 - 7.90 (m, 2 H)
1b-21	0.62 - 0.99 (m, 26 H), 1.16 - 1.78 (m, 22 H), 2.64 - 2.95 (m, 13 H), 2.98 - 3.13 (m, 3 H), 3.81 - 3.90 (m, 4 H), 4.38 - 4.49 (m, 1 H), 4.99 - 5.74 (m, 11 H), 7.08 - 7.31 (m, 10 H,) 7.42 - 7.53 (m, 2 H)
1b-22	0.62 - 0.99 (m, 26 H), 1.13 - 1.84 (m, 16 H), 2.61 - 2.97 (m, 13 H) 3.01 - 3.20 (m, 3 H) 4.34 - 4.53 (m, 1 H) 4.87 - 5.80 (m, 11 H) 7.16 - 7.39 (m, 8 H), 8.06 (s, 2 H), 8.47 (s, 2 H), 8.74 - 9.05 (m, 2 H), 10.82 - 11.15 (m, 2 H), 12.33 - 12.89 (m, 2 H)
1b-23	0.67-0.94 (m, 26H), 1.16-1.76 (m, 16 H), 2.65-3.09 (m, 16 H), 4.39-5.72 (m, 12 H), 6.24-6.26 (m, 2 H), 7.14 (d, 4 H), 7.27(dd, 4 H),7.43-7.45(m, 2 H), 7.74-7.77 (m, 2H)
1b-24	0.67-0.96 (m, 26H), 1.17-1.74 (m, 16 H), 1.98 (s, 6H), 2.64-3.07 (m, 16 H), 4.39-5.71 (m, 12 H), 7.13 (d, 4 H), 7.21-7.30 (m, 6 H), 7.47-7.50 (m, 2H)
1b-25	0.67-0.96 (m, 26H), 1.19-1.76 (m, 16 H), 2.65-3.09 (m, 16 H), 4.39-5.74 (m, 12 H), 7.19 (d, 4 H), 7.29 (dd, 4 H), 7.54-7.56 (m, 2 H), 8.01-8.03 (m, 2H)
1b-26	0.65-0.96 (m, 26H), 1.14-1.74 (m, 16 H), 2.65-3.09 (m, 16 H), 4.38-5.74 (m, 12 H), 7.14-7.35 (m, 14 H), 7.54 (d, 4 H), 7.87-7.91 (m, 2 H), 8.20-8.24 (m, 2H)

1b-27	0.64-0.97 (m, 26H), 1.14-1.74 (m, 16 H), 2.63-3.10 (m, 16 H), 4.38-5.73 (m, 12 H), 7.15-7.34 (m, 12 H), 7.53-7.59 (m, 4 H), 7.85-7.89 (m, 2 H), 8.18-8.24 (m, 2H)
1b-28	0.65-0.94 (m, 26H), 1.14-1.72 (m, 16 H), 2.64-3.12 (m, 16 H), 4.38-5.73 (m, 12 H), 7.18-7.31 (m, 8 H), 7.39 (d, 4 H), 7.58(dd, 4 H), 7.89-7.92(m, 2H), 8.25-8.29(m, 2 H)
1b-29	0.68-0.95 (m, 26H), 1.19-1.74 (m, 16 H), 2.05-2.15 (m, 12 H), 2.66-3.08 (m, 16 H), 4.38-5.71 (m, 12 H), 5.85 (s, 2 H), 7.01 (d, 4 H), 7.26 (dd, 4 H)
1b-30	0.67-0.95 (m, 26H), 1.17-1.74 (m, 34 H), 2.64-3.07 (m, 16 H), 4.38-5.73 (m, 12 H), 7.14 (d, 4 H), 7.23-7.34 (m, 6 H), 7.53-7.56 (m, 2H)
1b-31	0.65-0.95 (m, 26H), 1.11 (t, 6 H), 1.18-1.74 (m, 16 H), 2.40 (q, 4H), 2.65-3.08 (m, 16 H), 4.39-5.71 (m, 12 H), 7.14 (d, 4 H), 7.24-7.30 (m, 6 H), 7.50-7.53 (m, 2H)
1b-32	0.71 - 0.92 (m, 26 H), 1.27 - 1.69 (m, 16 H), 2.67 - 3.04 (m, 16 H), 3.97 (s, 2 H) 4.39 - 4.48 (m, 1 H), 5.09 - 5.69 (m, 11 H), 7.17 - 7.19 (m, 4 H), 7.28 - 7.30 (m, 4 H), 7.62 (s, 2 H), 8.09 (br s, 2 H)
1b-34	1H NMR (400 MHz, $CDCl_3$) δ: 0.83 - 0.93 (m, 20 H), 1.24 - 1.70 (m, 20 H), 2.64 - 3.09 (m, 18 H), 4.41 - 4.43 (m, 1 H), 5.27 - 5.61 (m, 11 H), 7.19 - 7.25 (m, 8 H), 7.52 - 7.78 (m, 4 H)
1b-35	0.67-0.95 (m, 26H), 1.17-1.73 (m, 16 H), 2.67-3.08 (m, 16 H), 4.39-5.72 (m, 12 H), 7.19 (d, 4 H), 7.29 (d, 4 H), 7.52-7.55 (m, 2H), 8.02-8.04 (m, 2 H)
1b-36	0.67-0.95 (m, 26H), 1.20-1.73 (m, 16 H), 1.84 (s, 6 H), 2.04-2.08 (m ,12 H), 2.67-3.07 (m, 16 H), 4.38-5.70 (m, 12 H), 7.02 (d, 4 H), 7.26 (d, 4 H)
1b-37	0.67-0.96 (m, 26H), 1.14 (d, 12 H), 1.22-1.76 (m, 16 H), 2.67-3.06 (m, 18 H), 4.39-5.72 (m, 12 H), 7.14 (d, 4 H), 7.25-7.32 (m, 8 H), 7.51-7.53 (m, 2 H)
1b-38	0.66-0.94 (m, 26H), 1.18-1.74 (m, 16 H), 2.34 (s, 6 H), 2.67-3.08 (m, 16 H), 4.39-5.72 (m, 12 H), 7.23 (d, 4 H), 7.30 (d, 4 H), 7.91-7.93 (m, 2 H), 8.47-8.49 (m, 2 H).
1b-39	0.67-0.95 (m, 26H), 1.19-1.76 (m, 22 H), 2.67-3.08 (m, 16 H), 4.19 (q, 4 H), 4.38-5.72 (m, 12 H), 7.23 (d, 4 H), 7.30 (d, 4 H), 7.83-7.85 (m, 2 H), 8.39-8.41 (m, 2 H)
1b-40	0.67-0.95 (m, 26H), 1.19-1.76 (m, 16 H), 2.67-3.08 (m, 16 H), 3.55-3.61 (m, 16 H), 4.39-5.72 (m, 12 H), 7.21 (d, 4 H), 7.29(d, 4 H), 7.69-7.71(m, 2 H), 8.19-8.21(m, 2H)
1b-41	0.67-0.94 (m, 26H), 1.19-1.94 (m, 24 H), 2.67-3.07 (m, 16 H), 3.41 (t, 4 H), 3.61 (t, 4 H), 4.39-5.72 (m, 12 H), 7.21 (d, 4 H), 7.29 (d, 4 H), 7.77-7.79 (m, 2 H), 8.26-8.28 (m, 2 H).
1b-42	0.67-0.94 (m, 26H), 1.19-1.75 (m, 28 H), 2.67-3.08 (m, 16 H), 3.51-3.54 (m, 8 H), 4.39-5.72 (m, 12 H), 7.21(d, 4 H), 7.29(d, 4 H), 7.63-7.65(m, 2 H), 8.11-8.13(m, 2 H)
1b-43	0.67-0.96 (m, 26H), 1.19-1.76 (m, 16 H), 2.08 (s, 6 H), 2.67-3.07 (m, 16 H), 4.39-5.72 (m, 12 H), 7.19 (d, 4 H), 7.28 (d, 4 H), 7.92-7.94 (m, 2 H).
1b-44	0.68-0.96 (m, 26H), 1.19-1.76 (m, 16 H), 2.08-2.13 (m, 12 H), 2.67-3.07 (m, 16 H), 4.39-5.70 (m, 12 H), 7.06 (d, 4 H), 7.28 (d, 4 H)
1b-45	0.41 - 0.44 (m, 4 H), 0.67 - 0.98 (m, 30 H), 1.23 - 1.74 (m, 18 H), 2.68 - 3.04 (m, 16 H), 4.39 - 4.45 (m, 1 H), 5.01 - 5.73 (m, 11 H), 7.12 - 7.15 (m, 4 H), 7.22 - 7.27 (m, 6 H), 7.49 - 7.51 (m, 2 H)
1b-46	0.67 - 0.94 (m, 27 H), 1.24 - 1.68 (m, 15 H), 2.67 - 3.12 (m, 16 H), 4.39 - 4.43 (m, 1 H), 5.02 - 5.71 (m, 13 H), 7.17 - 7.19 (m, 4 H), 7.28 - 7.29 (m, 4 H), 7.52 (brs, 2 H), 7.95 -7.60 (m, 2 H)
1b-47	0.65 - 0.94 (m, 30 H), 1.20 - 1.73 (m, 21 H), 2.33 - 2.36 (m, 4 H), 2.67 - 3.02 (m, 16 H), 4.37 - 4.48 (m, 1 H), 5.01 - 5.69 (m, 12 H), 7.11 -7.13 (m, 4 H), 7.26 (s, 6 H), 7.50 (s, 2 H)
1b-48	0.74 - 1.00 (m, 26 H), 1.21 - 1.69 (m, 20 H), 2.03 - 2.06 (m, 12 H), 2.25 - 2.30 (m, 5 H), 2.67 - 2.89 (m, 12 H), 3.01 - 3.05 (m, 4 H), 4.41 - 4.43 (m, 1 H), 5.08 - 5.68 (m, 12 H), 6.98 - 7.00 (m, 4 H), 7.24 - 7.26 (m, 4 H)
1b-49	0.67-0.94 (m, 26H), 1.18-1.76 (m, 28 H), 2.67-3.08 (m, 24 H), 4.39-5.73 (m, 12 H), 7.22 (d, 4 H), 7.31 (d, 4 H), 7.77-7.79 (m, 2 H), 8.44-8.46 (m, 2H)
1b-50	0.68-0.94 (m, 26H), 1.19-1.76 (m, 16 H), 2.67-3.09 (m, 24 H), 3.64-3.67 (m, 8 H), 4.39-5.73 (m, 12 H), 7.24 (d,4H), 7.32 (d,4H), 7.81-7.83 (m, 2 H), 8.49-8.51 (m, 2H)
1b-51	0.78 - 0.93 (m, 24 H), 1.23 - 1.69 (m, 17 H), 2.09 - 2.11 (m, 12 H), 2.67 - 3.02 (m, 16 H), 4.39 - 4.41 (m, 1 H), 5.01 - 5.68 (m, 12 H), 7.04 - 7.06 (d, *J* = 7.2 Hz, 4 H), 7.26 - 7.28 (d, *J* = 7.2 Hz, 4 H)
1b-52	0.66 - 0.94 (m, 24 H), 1.20 - 1.70 (m, 16 H), 2.67 - 3.03 (m, 16 H), 3.62 (s, 6 H), 4.39 - 4.42 (m, 1 H), 5.01 - 5.69 (m, 13 H), 7.07 - 7.52 (m, 12 H)

1b-53	1H NMR (400 MHz, $CDCl_3$) δ: 0.72 - 0.1.01 (m, 28 H), 1.02 - 1.47 (m, 12 H), 1.60 - 1.74 (m, 4 H), 2.73 - 3.17 (m, 18 H), 3.63 (s, 1 H), 4.42 - 4.45 (m, 1 H), 5.05 - 5.98 (m, 14 H), 7.15 - 7.23 (m, 8 H), 7.71 - 7.79 (m, 4 H)
1b-54	0.67-0.94 (m, 26H), 1.18-1.73 (m, 24 H), 2.67-3.11 (m, 24 H), 4.39-5.73 (m, 12 H), 7.21 (d, 4 H), 7.31 (d, 4 H), 7.86 (s, 2 H), 8.50-8.52 (m, 2H)
1b-55	0.69 - 0.94 (m, 24 H), 1.01 - 1.16 (m, 12 H), 1.29 - 1.36 (m, 12 H), 1.38 - 1.71 (m, 12 H), 2.66 - 3.01 (m, 24 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.66 (m, 13 H), 5.93 (s, 2 H), 6.97 - 6.99 (m, 4 H), 7.24 - 7.27 (m, 4 H)
1b-56	0.67 - 0.94 (m, 24 H), 1.25 - 1.80 (m, 16 H), 2.67 - 3.04 (m, 28 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.90 (m, 13 H), 7.20 - 7.30 (m, 8 H), 7.72 (s, 2 H), 8.20 (s, 2 H)
1b-57	0.79 - 0.94 (m, 30 H), 1.23 - 1.70 (m, 20 H), 2.03 -2.05 (m, 12 H), 2.24 (t, *J* = 6.2 Hz, 4 H), 2.67 - 3.01 (m, 16 H), 4.39 - 4.42 (m, 1 H), 5.10 - 5.67 (m, 13 H), 6.96 - 6.98 (m, 4 H), 7.24 - 7.25 (m, 4 H)
1b-58	0.69 - 0.92 (m, 24 H), 1.23 - 1.69 (m, 16 H), 2.32 (s, 6 H), 2.40 (s, 6 H), 2.67 - 3.09(m, 16 H), 4.39 - 4.42 (m, 1 H), 5.09 - 5.69 (m, 13 H), 7.13 - 7.15 (m, 4 H), 7.25 - 7.39 (m, 4 H)
1b-59	0.71 - 0.94 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.67 - 3.04 (m, 16 H), 3.18 (s, 6 H), 4.39 - 4.42 (m, 1 H), 5.08 - 571 (m, 13 H), 7.25 - 7.32 (m, 8 H), 7.91 (s, 2 H), 8.49 - 8.50 (m, 2 H)
1b-60	0.76 - 0.94 (m, 24 H), 1.12 - 1.13 (m, 12 H), 1.23 - 1.69 (m, 18 H), 2.67 - 3.03 (m, 16 H), 4.38 - 4.41 (m, 1 H), 5.10 - 5.70 (m, 13 H), 7.14 - 7.16 (m, 4 H), 7.27 - 7.29 (m, 4 H), 7.46 (s, 2 H), 7.91 (s, 2 H)
1b-61	0.67-0.95 (m, 26H), 1.19-1.73 (m, 16 H), 1.96- 2.01 (m, 4 H), 2.67-3.07 (m, 16 H), 3.61-3.63 (m, 8 H), 4.39-5.73 (m, 12 H), 7.24 (d, 4 H), 7.32 (d, 4 H), 7.92 (s, 2 H), 8.58-8.60 (m, 2H)
1b-62	0.68-0.97 (m, 26H), 1.18-1.72 (m, 16 H), 2.67-3.07 (m, 16 H), 4.39-5.71 (m, 12 H), 7.00 (t, 2 H), 7.20 (d, 4 H), 7.30 (d, 4 H), 7.68 (s, 2 H), 8.14-8.16 (m, 2H)
1b-63	0.68-0.96 (m, 26H), 1.19-1.72 (m, 16 H), 2.67-3.07 (m, 16 H), 4.39-5.72 (m, 12 H), 6.37-6.39 (m, 2 H), 7.19 (d, 4 H), 7.29 (d, 4 H), 7.84-7.86 (m, 2H)
1b-64	0.68-0.94 (m, 26H), 1.18-1.72 (m, 16 H), 2.67-3.07 (m, 16 H), 4.39-5.71 (m, 12 H), 6.45-6.47 (m, 2 H), 7.17-7.20 (m, 4 H), 7.29-7.32 (m, 4 H), 7.73-7.75 (m, 2H)
1b-65	0.67 - 0.94 (m, 24 H), 1.21 - 1.70 (m, 16 H), 2.04 - 2.05 (m, 12 H), 2.43 (t, *J* = 7.3 Hz, 4 H), 2.67 - 3.01 (m, 16 H), 3.35 - 3.37 (m, 4 H), 4.39 - 4.41 (m, 1 H), 4.53 - 4.56 (m, 2 H), 5.08 - 5.68 (m, 13 H), 6.99 - 7.01 (m, 4 H), 7.24 - 7.26 (m, 4 H)
1b-66	0.67 - 0.93 (m, 26 H), 1.23 - 1.78 (m, 16 H), 2.69 - 3.12 (m, 16 H), 4.39 - 4.42 (m, 1 H), 4.91 - 5.71 (m, 11 H), 7.22 - 7.24 (m, 4 H), 7.35 - 7.38 (m, 4 H), 7.98 (s, 2 H)
1b-67	0.54-0.59 (m, 4 H), 0.68-0.96 (m, 30H), 1.17-1.84 (m, 18 H), 2.67-3.07 (m, 16 H), 4.39-5.70 (m, 12 H), 5.92 (s, 2 H), 7.12 (d, 4 H), 7.26 (d, 4 H), 7.59 (s, 2H)
1b-68	0.67-0.96 (m, 26H), 1.18-1.76 (m, 16 H), 2.63-3.07 (m, 16 H), 4.38-5.72 (m, 12 H), 6.71-6.73 (m, 2 H), 7.20-7.40 (m, 14 H), 7.76 (d, 4 H), 7. 84-7.86 (m, 2H)
1b-69	0.67-0.94 (m, 26H), 1.17-1.76 (m, 16 H), 2.67-3.08 (m, 16 H), 4.38-5.73 (m, 12 H), 6.72 (s, 2 H), 7.22 (d, 4 H), 7.31 (d, 4 H), 8.06 (s, 2H)
1b-70	0.66 - 0.93 (m, 24 H), 1.20 - 1.70 (m, 17 H), 2.67 - 3.08 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.71 (m, 12 H), 7.28 - 7.33 (m, 8 H), 8.26 (s, 2 H), 8.99 - 9.00 (m, 2 H)
1b-71	0.67 - 0.93 (m, 24 H), 1.17 - 1.67 (m, 17 H), 2.65 - 3.04 (m, 16 H), 4.37 - 4.43 (m, 1 H), 5.06 - 5.70 (m, 12 H), 7.14 - 7.15 (m, 2 H), 7.17 - 7.23 (m, 4 H), 7.25 - 7.31 (m, 4 H), 7.61 - 7.63 (m, 2 H), 7.72 - 7.75 (m, 2 H), 8.01 - 8.02 (m, 2 H), 8.33 - 8.34 (m, 2 H), 8.47 - 8.48 (m, 2 H)
1b-72	0.67 - 0.94 (m, 24 H), 1.23 - 1.70 (m, 17 H), 1.94 (s, 6 H), 2.67 - 3.03 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.07 - 5.72 (m, 12 H), 7.13 - 7.15 (m, 4 H), 7.17 - 7.18 (m, 1 H), 7.26 - 7.27 (m, 3 H), 7.36 (s, 2 H), 7.89 - 7.90 (m, 2 H), 9.91 (s, 2 H)
1b-74	0.44 - 0.48 (m, 4 H), 0.62 - 0.94 (m, 28 H), 1.21 - 1.69 (m,17 H), 2.67 - 3.04 (m, 18 H), 4.37 - 4.48(m, 1 H), 5.02 - 5.70(m, 12 H), 7.18 - 7.30(m, 8 H), 7.81 - 8.14(m, 6H)
1b-75	0.67 - 0.94 (m, 26 H), 1.21 - 1.70 (m, 17 H), 2.67 - 3.03 (m, 18 H), 3.46 - 3.51 (m, 4 H), 4.37 - 4.45 (m, 1 H), 4.58 (t, *J* = 5.2 Hz, 2 H), 5.08 - 5.69 (m, 12 H), 7.13 - 7.15 (m, 4 H), 7.25 - 7.27 (m, 6 H), 7.52 (brs, 2 H
1b-76	0.60 - 0.95 (m, 24 H), 1.15 - 1.80 (m, 18 H), 2.65 - 3.20 (m, 22 H), 4.35 - 4.45 (m, 1 H), 5.00 - 5.80 (m, 11 H), 7.10 - 7.35 (m, 10 H), 7.69 (s, 2 H), 9.11 (s, 2 H)

1b-77	0.66-0.96 (m, 26H), 1.14-1.73 (m, 16 H), 2.64-3.11 (m, 16 H), 4.38-5.80 (m, 12 H), 7.41 (d, 4 H), 7.57-7.60 (m, 4 H), 8.12-8.15 (m, 2H), 8.39 (s, 4 H), 8.80 (d, 2 H), 8.93-8.97 (m, 2 H), 9.58 (s, 2 H)
1b-78	0.67-0.95 (m, 26H), 1.17-1.73 (m, 28 H), 1.89-1.96 (m ,4 H), 2.67-3.07 (m, 18 H), 4.39-5.71 (m, 12 H), 7.14 (d, 4 H), 7.24-7.30 (m, 6 H), 7.51-7.53 (m, 2H)
1b-79	0.67-0.95 (m, 26 H), 1.15-1.73 (m, 28 H), 2.67-3.07 (m, 18 H), 4.39-5.71 (m, 12 H), 6.06 (s, 2 H), 7.12 (d, 4 H), 7.26 (d, 4 H), 7.59 (s, 2H)
1b-80	0.68-0.94 (m, 26H), 1.20-1.76 (m, 24 H), 2.29 (s, 6 H), 2.39 (s, 6 H), 2.67-3.09 (m, 24 H), 4.39-5.71 (m, 12 H), 7.06 (d, 4 H), 7.30 (d, 4 H)
1b-81	0.67-0.94 (m, 26H), 1.19-1.74 (m, 34 H), 2.67-3.07 (m, 16 H), 4.39-5.71 (m, 12 H), 6.10 (s, 2 H), 7.11 (d, 4 H), 7.26 (d, 4 H), 7.55-7.57 (m, 2H)
1b-82	0.68 - 0.93 (m, 24 H), 1.25 - 1.89 (m, 16 H), 2.65 - 3.03 (m, 16 H), 4.38 - 4.40 (m, 1 H), 5.02 - 5.67 (m, 13 H), 6.60 (brs, 2 H), 7.20 - 7.29 (m, 8 H), 7.43 - 7.44 (m, 2 H), 7.55 (brs, 2 H), 7.71 (s, 2 H), 7.79 (s, 2 H)
1b-83	0.65 - 0.95 (m, 24 H), 1.02 - 1.75 (m, 18 H), 2.65 - 3.05 (m, 16 H), 4.30 - 4.45 (m, 8 H), 4.85 - 5.75 (m, 16 H), 6.14 (s, 2 H), 7.05 - 7.10 (m, 4H), 7.25 - 7.30 (m, 4H)
1b-84	0.65 - 0.98 (m, 24 H), 1.20 - 1.80 (m, 18 H), 1.98 - 2.00 (m, 18 H), 2.60 - 3.10 (16 H) , 4.38 - 4.42 (m, 1 H), 4.85 - 5.60 (m, 11 H), 7.00 (d, *J* = 7.8 Hz, 4 H), 7.28 (d, *J* = 7.0 Hz, 4 H) 8.95 (s, 2 H)
1b-85	0.69-0.94 (m, 26H), 1.19-1.76 (m, 28 H), 2.27 (s, 6 H), 2.36 (s, 6 H), 2.67-3.09 (m, 24 H), 4.39-5.71 (m, 12 H), 7.06 (d, 4 H), 7.30 (d, 4 H)
1b-86	0.72 - 0.91 (m, 24 H), 1.15 - 1.80 (m, 17 H), 2.65 - 3.05 (m, 16 H), 4.41 - 4.45 (m, 1 H), 5.00 - 5.70 (m, 12 H), 7.24 - 7.36 (m, 8 H), 7.71 - 7.73 (m, 2 H), 8.18 - 8.21 (m, 2 H), 8.57 - 8.60 (m, 2 H), 8.67 - 8.69 (m, 2 H), 9.03 (s, 2 H)
1b-87	0.72 - 0.92 (m, 24 H), 1.19 - 1.67 (m, 16 H), 2.65 - 3.04 (m, 16 H), 4.35 - 4.45 (m, 2 H), 5.01 - 5.75 (m, 12 H), 7.24 - 7.31 (m, 8 H), 8.14 (s,2 H), 8.40 (s, 2 H), 8.49 - 8.53 (m, 4 H), 8.96 (s, 2 H)
1b-88	0.65 - 0.94 (m, 24 H), 1.23 - 1.70 (m, 17 H), 1.79 (s, 6 H), 2.68 - 3.03 (m, 16 H), 4.04 (d, *J* = 5.4 Hz, 4 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 12 H), 7.15 -7.17 (m, 4 H), 7.26 - 7.28 (m, 4 H), 7.33 (s, 2 H), 7.62 (s, 2 H), 8.09 (brs, 2 H)
1b-89	0.67 - 0.93 (m, 24 H), 1.23 - 1.79 (m, 16 H), 2.66 - 3.04 (m, 16 H), 3.85 - 3.95 (m, 1 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 12 H), 6.89 - 7.5 (m, 14 H)
1b-90	0.69 - 0.94 (m, 24 H), 1.15 - 1.75 (m, 17 H), 2.67 - 3.04 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 12 H), 6.97 (s, 2 H), 7.18 - 7.31 (m, 8 H), 7.51 (s, 2 H), 7.83 (s, 2 H), 8.14 - 8.15 (s, 2 H)
1b-91	0.67 - 0.94 (m, 24 H), 1.20 - 1.75 (m, 35 H), 2.68 - 3.02 (m, 16 H), 3.92 - 3.94 (m, 4 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.69 (m, 12 H), 7.11 -7.15 (m, 6 H), 7.25 - 7.32 (m, 6 H), 7.57 - 7.58 (m, 2 H)
1b-92	0.70 - 0.95 (m, 24 H), 1.23 - 1.71 (m, 16 H), 2.26 (s, 6 H), 2.34 (s, 6 H), 2.67 - 3.03 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.03 - 5.76 (m, 13 H), 7.07 - 7.18 (m, 8 H), 7.28 - 7.30 (m, 4 H)
1b-94	0.66 - 0.92 (m, 24 H), 1.21 - 1.68 (m, 16 H), 2.10 (s, 6 H), 2.65 - 3.00 (m, 16 H), 4.37 - 4.40 (m, 1 H), 5.01 - 5.67 (m, 13 H), 5.98 (s, 2 H), 7.10 - 7.12 (m, 4 H), 7.23 - 7.25 (m, 4 H), 7.59 (s, 2 H)
1b-95	0.71 - 0.93 (m, 24 H), 1.09 - 1.70 (m, 22 H), 2.67 - 3.02 (m, 20 H), 4.39 - 4.41 (m, 1 H), 5.01 - 5.66 (m, 13 H), 6.05 (s, 2 H), 7.12 - 7.14 (m, 4 H), 7.24 - 7.26 (m, 4 H), 7.61 (s, 2 H)
1b-96	0.69 - 0.94 (m, 24 H), 1.24 - 1.69 (m, 16 H), 2.67 - 3.03 (m, 16 H), 4.39 - 4.41 (m, 1 H), 5.01 - 5.67 (m, 13 H), 6.44 (s, 2 H), 7.06 - 7.08 (m, 4 H), 7.26 - 7.28 (m, 4 H), 7.58 (s, 2 H)
1b-97	0.75 - 0.95 (m, 24 H), 1.27 - 1.70 (m, 16 H), 2.67 - 3.02 (m, 16 H), 4.35 - 4.37 (m, 4 H), 4.94 - 5.70 (m, 16 H), 6.18 (brs, 2 H), 7.14 - 7.16 (m, 4 H), 7.26 - 7.28 (m, 4 H), 7.67 (brs, 2 H)
1b-98	0.67 - 0.95 (m, 24 H), 1.19 - 1.70 (m, 17 H), 2.68 - 3.03 (m, 16 H), 3.86 - 3.87 (m, 4 H), 4.40 - 4.43 (m, 1 H), 5.07 - 5.71 (m, 12 H), 7.17 - 7.28 (m, 8 H), 7.54 (s, 2 H), 7.85 (s, 2 H), 8.08 (brs, 6 H)
1b-99	0.86 - 0.94 (m, 24 H), 1.23 - 1.67 (m, 18 H), 1.94 (s, 6 H), 2.67 - 3.03 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.69 (m, 11 H), 6.45 (s, 2 H), 7.15 - 7.17 (m, 4 H), 7.26 - 7.28 (m, 4 H), 7.64 (brs, 2 H), 10.36 (s, 2 H)

1b-100	0.72 - 0.93 (m, 24 H), 1.08 - 1.33 (m, 12 H), 1.46 (s, 18 H), 1.61 - 1.92 (m, 4 H), 2.66 - 3.02 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.02 - 5.66 (m, 13 H), 6.83 (s, 2 H), 7.01 - 7.03 (m, 4 H), 7.25 - 7.26 (m, 4 H), 7.58 (s, 2 H)
1b-101	0.70 - 0.95 (m, 24 H), 1.23 - 1.68 (m, 17 H), 2.68 - 3.05 (m, 16 H), 4.40 - 4.43 (m, 1 H), 5.03 - 5.68 (m, 12 H), 7.24 - 7.30 (m, 12 H), 7.71 (s, 2 H), 8.25 (brs, 2 H)
1b-102	0.68 - 0.94 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.67 - 3.07 (m, 16 H), 4.38 - 4.40 (m, 1 H), 5.04 - 5.74 (m, 13 H), 7.20 - 7.46 (m, 18 H), 7.71 (brs, 2 H), 8.15 - 8.17 (m, 2 H)
1b-103	0.67 - 0.93 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.67 - 3.09 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.03 - 5.71 (m, 13 H), 6.98 (s, 2 H), 7.22 - 7.24 (m, 4 H), 7.30 - 7.32 (m, 4 H), 8.13 (s, 2 H)
1b-104	0.66 - 0.94 (m, 24 H), 1.23 - 1.57 (m, 22 H), 2.67 - 3.10 (m, 16 H), 4.08 (q, *J* = 6.8 Hz, 4 H), 4.41 - 4.43 (m, 1 H), 5.05 - 5.70 (m, 13 H), 6.96 (s, 1 H), 7.04 - 7.09 (m, 5 H), 7.21 - 7.26 (m, 6 H)
1b-105	0.70 - 0.94 (m, 24 H), 1.23 - 1.69 (m, 15 H), 2.67 - 3.02 (m, 24 H), 3.65 (brs, 8 H), 4.40 - 4.42 (m, 1 H), 5.02 - 5.73 (m, 14 H), 7.10 - 7.12 (m, 5 H), 7.24 - 7.25 (m, 5 H), 7.54 (brs, 2 H)
1b-106	0.68 - 0.93 (m, 26 H), 1.27 - 2.19 (m, 27 H), 2.67 - 3.02 (m, 16 H), 3.46 - 3.49 (m, 2 H), 4.40 - 4.42 (m, 1 H), 4.94 - 5.86 (m, 12 H), 6.12 (brs, 2 H), 7.12 - 7.14 (m, 4 H), 7.26 - 7.27 (m, 4 H), 7.62 (brs, 2 H)
1b-107	0.72 - 0.93 (m, 24 H), 1.26 - 1.75 (m, 16 H), 2.66 - 3.04 (m, 16 H), 4.03 (s, 6 H), 4.38 - 4.41 (m, 1 H), 5.03 - 5.6.8 (m, 13 H), 7.12 - 7.23 (m, 4 H), 7.29 - 7.30 (m, 4 H), 7.76 (s, 2 H), 8.09 - 8.14 (m, 4 H)
1b-108	0.50-0.55 (m, 4 H), 0.68-0.94 (m, 30H), 1.18-1.79 (m, 18 H), 2.67-3.06 (m, 16 H), 4.38-5.70 (m, 12 H), 5.90 (s, 2 H), 7.06 (d, 4 H), 7.26 (d, 4 H), 7.32 (s, 2H)
1b-109	0.56 - 1.02 (m, 26 H) 1.04 - 1.84 (m, 16 H) 2.27 (m, 4 H) 2.55 - 3.11 (m, 16 H) 3.42 - 3.66 (m, 2 H) 3.75 (m, 4 H) 4.13 (m, 4 H) 4.41 (m, 1 H) 4.92 - 5.77 (m, 9 H) 5.96 (m, 2 H) 7.01 - 7.42 (m, 8 H) 7.60 (m, 2H), 7.83 (m, 2 H)
1b-110	0.70 - 0.94 (m, 24 H), 1.24 - 1.69 (m, 16 H), 2.08 -2.09 (m, 12 H), 2.67 - 3.02 (m, 16 H), 4.40 - 4.42(m, 1 H), 5.03 - 5.68(m, 13H), 7.02 - 7.04 (m, 4H), 7.25 -7.27 (m, 4 H)
1b-111	0.72 - 0.92 (m, 24 H), 1.16 - 1.69 (m, 16 H), 2.66 - 3.03 (m, 16 H), 4.38 - 4.41 (m, 1 H), 5.01 - 5.67 (m, 13 H), 6.48 (brs, 2 H), 6.75 (s, 2 H), 7.17 - 7.18 (m, 4 H), 7.27 - 7.29 (m, 4 H), 7.67 (s, 2 H), 7.78 (s, 2 H), 7.98 (s, 2 H)
1b-112	0.69 - 0.93 (m, 26 H), 1.14 - 1.69 (m, 27 H), 2.67 - 3.03 (m, 16 H), 4.38 - 4.41 (m, 1 H), 5.02 - 5.69 (m, 14 H), 7.15 - 7.17 (m, 4 H), 7.27 -7.29 (m, 4 H), 7.51 (brs, 2 H), 7.94 (brs, 2 H)
1b-113	0.62 - 0.94 (m, 32 H), 1.23 - 1.69 (m, 18 H), 2.67 - 3.04 (m, 16 H), 4.39 - 4.41 (m, 1 H), 5.03 - 5.69 (m, 13 H), 7.14 - 7.16 (m, 4 H), 7.27 - 7.29 (m, 4 H), 7.50 (s, 2 H), 7.93 - 7.94 (m, 2 H)
1b-114	0.68 - 0.94 (m, 26 H), 1.23 - 1.69 (m, 33 H), 2.67 - 3.04 (m, 16 H), 4.42 - 4.44 (m, 1 H), 5.09 - 5.69 (m, 12 H), 7.15 - 7.17 (m, 4 H), 7.27 -7.29 (m, 4 H), 7.49 - 7.50 (m, 2 H), 7.92 - 7.93 (m, 2 H)
1b-115	0.67 - 0.94 (m, 24 H), 1.24 - 1.69 (m, 17 H), 2.67 - 3.06 (m, 16 H), 3.82 (s, 6 H), 4.38 - 4.41 (m, 1 H), 5.05 - 5.68 (m, 14 H), 7.02 - 7.04 (m, 4 H), 7.25 - 7.27 (m, 6 H)
1b-116	0.60-1.04 (m, 26H), 1.04-1.84 (m, 20H), 2.58-3.15 (m, 16H), 3.37-3.45 (m, 4H), 3.79-3.91 (m, 4H), 4.35-4.59 (m, 1H), 4.97-5.79 (m, 11H), 7.02-7.35 (m, 8H), 7.50-7.72 (m, 2H), 7.50-7.72 (m, 2H)
1b-117	0.69 - 0.93 (m, 23 H), 1.23 - 1.83 (m, 19 H), 2.21 – 2.32 (m, 12 H), 2.67 - 3.18 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.09 - 5.67 (m, 11 H), 7.11 (d, J = 7.5 Hz, 4 H), 7.29 (d, J = 6.9 Hz, 4 H)
1b-118	0.67 - 0.94 (m, 26 H), 1.20 - 1.70 (m, 16 H), 1.96 (s, 6 H), 2.67 - 3.04 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.00 - 5.75 (m, 11 H), 7.15 - 7.96 (m, 12 H)
1b-119	0.67 - 0.94 (m, 26 H), 1.10 (t, J = 7.4 Hz, 6 H,), 1.21 - 1.75 (m, 16 H), 2.31 - 2.37 (m, 4 H), 2.67 - 3.04 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.00 - 5.75 (m, 11 H), 7.15 - 7.96 (m, 12 H)
1b-120	0.66 - 0.92 (m, 26 H), 1.15 - 1.70 (m, 16 H), 2.64 - 3.03 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.72 (m, 11 H), 6.82 (s, 2 H), 7.22 - 8.55 (m, 18 H)
1b-121	0.66 - 0.92 (m, 26 H), 1.23 - 1.72 (m, 16 H), 2.66 - 3.05 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.71 (m, 11 H), 7.06 - 8.14 (m, 12 H)

1b-122	0.70 - 1.78 (m, 60 H), 2.42 - 2.45 (m, 2 H), 2.67 - 3.03 (m, 16 H), 4.41 - 4.45 (m, 1 H), 5.01 - 5.69 (m, 11 H), 7.08 - 7.09 (m, 4 H), 7.28 - 7.29 (m, 4 H)
1b-123	0.73 - 0.84 (m, 28 H), 0.92 - 0.96 (m, 12 H), 1.10 - 1.84 (m, 14 H), 2.65 - 3.03 (m, 24 H), 4.40 - 4.45 (m, 1 H), 5.00 - 5.67 (m, 11 H), 7.17 (bs, 4H), 7.31 (bs, 4 H)
1b-126	0.70-0.94 (m, 26 H), 1.07 (d, 12 H), 1.22-1.76 (m, 16 H), 2.66-3.06 (m, 18 H), 4.39-5.69 (m, 12 H), 6.11 (s, 2 H), 7.00 (d, 4 H), 7.24-7.27 (m, 4 H), 7.38 (s, 2 H)
1b-127	0.67-0.96 (m, 26 H), 1.22-1.76 (m, 34 H), 2.66-3.05 (m, 16 H), 4.39-5.67 (m, 12 H), 6.09 (s, 2 H), 6.88 (d, 4 H), 7.23-7.26 (m, 4 H), 7.38 (s, 2H)
1b-128	0.63-0.94 (m, 26 H), 1.22-1.76 (m, 16 H), 2.66-3.04 (m, 16 H), 4.39-5.68 (m, 12 H), 6.46 (s, 2 H), 6.88 (d, 4 H), 7.22-7.26 (m, 4 H), 7.39-7.42 (m, 10 H), 7.58 (s, 2 H)
1b-129	0.67-0.96 (m, 26 H), 1.22-1.92 (m, 24 H), 2.13-2.17 (m, 4 H), 2.65-3.05 (m, 16 H), 3.44-3.47 (m, 2 H), 4.39-5.67 (m, 12 H), 6.20 (s, 2 H), 6.97 (d, 4 H), 7.24-7.27 (m, 4 H), 7.38 (s, 2 H)
1b-130	0.67 - 0.91 (m, 25 H), 1.23 - 1.67 (m, 17 H), 2.20 (s, 6 H), 2.27 (s, 6 H), 2.67 - 3.03 (m, 16 H), 4.40 - 4.45 (m, 1 H), 5.08 - 5.69 (m, 11 H), 7.08 - 7.09 (m, 4 H), 7.28 – 7.30 (m, 4 H)
1b-133	0.65 - 0.95 (m, 30 H), 1.11 (t, J = Hz, 6 H), 1.21 - 1.72 (m, 18 H), 2.42 - 2.45 (m, 8 H), 2.66 - 3.00 (m,16H), 4.35-4.45 (m,1H), 5.01- 5.68 (m, 15 H), 6.94 - 7.23 (m, 8 H)
1b-134	0.67-0.93 (m, 26 H), 1.15-1.72 (m, 16 H), 2.63-3.09 (m, 16 H), 3.76 (s, 6 H), 4.39-5.72 (m, 12 H), 6.62 (s, 2 H), 6.89-6.96 (m, 4 H), 7.19-7.31 (m, 8 H), 7.68 (d, 4 H), 7.79 (s, 2 H)
1b-136	0.67 - 0.94 (m, 28 H), 1.18 - 1.37 (m, 8 H), 1.42 - 1.63 (m, 5 H), 1.65 - 1.72 (m, 2 H), 2.10 (s, 6 H), 2.68 (s, 2 H), 2.75 (d, 4 H), 2.85 (s, 2 H), 2.91 (br d, 5 H), 3.00 - 3.11 (m, 3 H), 4.16 - 4.44 (m, 1 H), 5.00 - 5.24 (m, 4 H), 5.30 - 5.54 (m, 6 H), 5.65 - 5.74 (m, 1 H), 7.23 (d, 4 H), 7.31 (br d, 4 H), 7.91 (s, 2 H)
1b-138	0.66 - 0.92 (m, 26 H), 1.00 - 1.74 (m, 16 H), 2.64 - 3.03 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.00 - 5.72 (m, 11 H), 6.92 (s, 2 H), 7.21 - 8.55 (m, 18 H)
1b-139	0.66 - 0.92 (m, 26 H), 1.00 - 1.74 (m, 16 H), 2.64 - 3.03 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.00 - 5.72 (m, 11 H), 6.92 (s, 2 H), 7.21 - 8.55 (m, 18 H)
1b-140	0.60-1.01 (m, 26H), 1.12-1.87 (m, 16H), 2.58-3.16 (m, 16H), 4.33-4.52 (m, 2H), 4.93-5.81 (m, 12H), 7.07-7.35 (m, 8H), 7.37-7.49 (m, 2H), 7.74-8.00 (m, 2H)
1b-141	0.57-1.00 (m, 26H), 1.11-1.78 (m, 16H), 1.86-2.09 (m, 4H), 2.20-2.40 (m, 4H), 2.63-3.16 (m, 16H), 4.24-4.53 (m, 5H), 4.96-5.83 (m, 12H), 7.02-7.34 (m, 8H), 7.37-7.57 (m, 2H)
1b-142	0.58-1.01 (m, 26H), 1.07-1.92 (m, 16H), 2.62-3.16 (m, 16H), 4.36-4.55 (m, 5H), 4.71-4.92 (m, 4H), 4.92-5.79 (m, 14H), 7.04-7.37 (m, 10H), 7.47-7.57 (m, 2H)
1b-143	0.70 - 0.95 (m, 26 H), 1.20 - 1.88 (m, 16 H), 2.68 - 3.02 (m, 16 H), 4.40 - 4.50 (m, 1 H), 4.51 (bs, 4 H), 4.98 - 5.69 (m, 13 H), 7.10 - 7.35 (m, 10 H)
1b-144	0.70 - 0.95 (m, 26 H), 1.20 - 1.88 (m, 16 H), 2.68 - 3.02 (m, 16 H), 4.40 - 4.50 (m, 1 H), 4.51 (bs, 4 H), 4.98 - 5.69 (m, 13 H), 7.10 - 7.35 (m, 10 H)
1b-145	0.70 - 0.95 (m, 26 H), 1.20 - 1.88 (m, 16 H), 2.68 - 3.02 (m, 16 H), 4.40 - 4.50 (m, 1 H), 4.51 (bs, 4 H), 4.98 - 5.69 (m, 13 H), 7.10 - 7.35 (m, 10 H)
1b-146	0.19 - 0.34 (m, 4 H), 0.46 - 0.61 (m, 4 H), 0.69 - 0.97 (m, 24 H), 1.11 - 1.32 (m, 8 H), 1.35 - 1.40 (m, 1 H), 1.42 - 1.64 (m, 5 H), 1.66 - 1.76 (m, 1 H), 2.69 (s, 2 H), 2.77 (d, 4 H), 2.83 - 2.96 (m, 6 H), 3.01 - 3.22 (m, 3 H), 3.37 (br s, 8 H), 3.64 (d, 4 H), 4.98 - 5.17 (m, 6 H), 5.23 (br dd, 1 H), 5.32 - 5.56 (m, 2 H), 5.64 - 5.75 (m, 1 H), 7.12 - 7.31 (m, 10 H), 7.46 - 7.51 (m, 2 H)
1b-148	0.65 - 0.94 (m, 26 H), 1.23 - 1.90 (m, 30 H), 2.67 - 3.02 (m, 18 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.70 (m, 13 H), 6.05 (s, 2 H), 7.11 - 7.60 (m, 10 H)
1b-149	0.64-0.94 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.06 (m, 16 H), 3.77 (s, 6 H), 4.39-5.72 (m, 12 H), 6.38 (s, 2 H), 6.88-6.98 (m, 8 H), 7.20-7.33 (m, 8 H), 7.54 (s, 2 H)
1b-151	0.68 - 0.94 (m, 27 H), 1.23 - 1.70 (m, 27 H), 2.67 - 3.01 (m, 16 H), 4.42 - 4.43 (m, 3 H), 5.02 - 5.67 (m, 11 H), 7.04 (m, 4 H), 7.25 - 7.35 (m, 8 H)
1b-152	0.68-0.94 (m, 26 H), 1.18-1.77 (m, 16 H), 1.91 (s, 6 H), 2.04 (s 6 H), 2.67-3.06 (m, 16 H), 4.39-5.71 (m, 12 H), 7.00 (d, 4 H), 7.21-7.27 (m, 6 H)
1b-153	0.63-0.93 (m, 26 H), 1.17-1.76 (m, 16 H), 2.67-3.05 (m, 16 H), 4.38-5.69 (m, 12 H), 6.49 (s, 2 H), 6.88 (d,4H), 7.19-7.24 (m,4H), 7.42 (d,4H), 7.49 (d, 4 H), 7.59 (s, 2 H)
1b-154	0.67-0.95 (m, 26 H), 1.19-1.74 (m, 28 H), 1.81-1.91 (m ,4 H), 2.67-3.06 (m, 18 H), 4.39-5.69 (m, 12 H), 6.10 (s, 2 H), 7.00 (d, 4 H), 7.23-7.28 (m, 4 H), 7.37 (s, 2H)

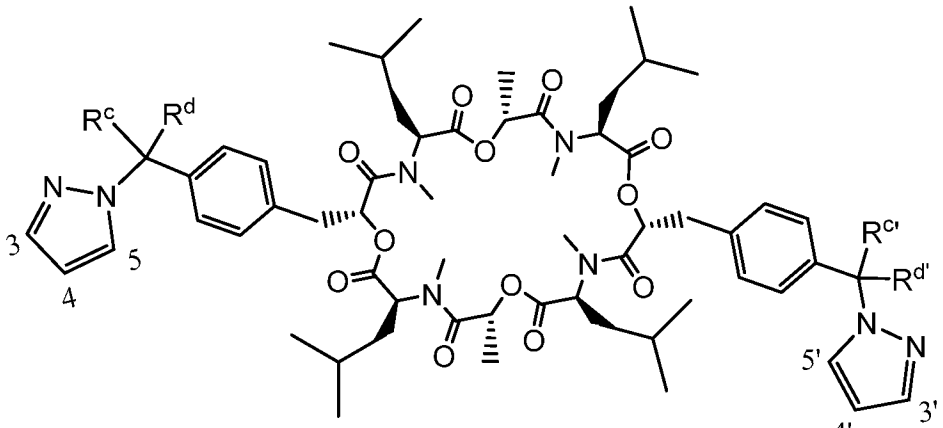
1b-155	0.67-0.95 (m, 26 H), 1.17-1.74 (m, 16 H), 2.67-3.07 (m, 16 H), 3.19 (s, 6 H), 4.24 (s, 4 H), 4.39-5.70 (m,12H), 7.12-7.18(m,4H), 7.25-7.30(m,4H), 7.40(s,2H), 7.73 (s,2H)
1b-156	0.65 - 0.94 (m, 26 H), 1.20 - 1.75 (m, 16 H), 2.67 - 3.04 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.00 - 5.72 (m, 11 H), 5.98 (s, 2 H), 6.99 - 7.78 (m, 12 H)
1b-157	0.67-0.94 (m, 26 H), 1.09 (t, 6 H), 1.18-1.76 (m, 16 H), 2.67-3.08 (m, 16 H), 3.40 (q, 4 H), 4.28 (s, 4 H), 4.39-5.72 (m, 12 H), 7.15 (d, 4 H), 7.27 (d, 4 H), 7.39 (s, 2 H), 7.71-7.73 (m, 2 H)
1b-158	0.68-0.95 (m, 26 H), 1.18-1.76 (m, 16 H), 2.09 (s, 6 H), 2.68-3.07 (m, 16 H), 4.26 (s, 4 H), 4.39-5.72 (m, 12 H), 7.15 (d, 4 H), 7.27 (d, 4 H), 7.52-7.54 (m, 2 H)
1b-159	0.65-0.95 (m, 26 H), 1.17-1.76 (m, 22 H), 2.05 (s, 6 H), 2.68-3.07 (m, 16 H), 4.07 (q, 4 H), 4.39-5.72 (m, 14 H), 7.05 (d, 4 H), 7.24-7.27 (m, 4 H)
1b-160	0.68-0.94 (m, 26 H), 1.18-1.74 (m, 16 H), 2.16 (s, 6 H), 2.67-3.07 (m, 16 H), 4.39-5.70 (m, 12 H), 6.06 (s, 2 H), 7.01 (d, 4 H), 7.26 (d, 4 H), 7.34 (s, 2 H)
1b-161	0.67 - 0.94 (m, 26 H), 1.33 - 2.40 (m, 28 H), 2.78 - 3.02 (m, 16 H), 4.40 - 4.50 (m, 1 H), 4.62 - 4.72 (m, 2H), 5.0-5.60 (m, 13 H), 7.12 (d, J = 7.7 Hz, 4 H), 7.26 (d, J = 7.9 Hz, 4 H), 7.53 - 7.55 (m, 2 H)
1b-162	0.68-0.94 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.08 (m, 16 H), 4.39-5.73 (m, 16 H), 7.24 (d, 4 H), 7.31 (d, 4 H), 7.91 (s, 2 H)
1b-163	0.68-0.95 (m, 26 H), 1.16-1.75 (m, 22 H), 2.05 (s, 6 H), 2.68-3.06 (m, 16 H), 4.07 (q, 4 H), 4.39-5.72 (m, 14 H), 7.05 (d, 4 H), 7.24-7.27 (m, 4 H)
1b-164	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 28 H), 2.05 (s, 6 H), 2.67-3.06 (m, 16 H), 4.37-5.71 (m, 16 H), 7.05 (d, 4 H), 7.23-7.27 (m, 4 H)
1b-165	0.68-0.94 (m, 26 H), 1.09 (t, 6 H), 1.18-1.76 (m, 16 H), 2.48-2.54 (m, 4 H), 2.67-3.07 (m,16H), 4.39-5.70 (m, 12 H), 6.09 (s, 2 H), 7.00 (d, 4 H), 7.26 (d, 4 H), 7.37 (s, 2 H)
1b-166	0.68-0.95 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.06 (m, 16 H), 3.20 (s, 6 H), 4.39-5.71 (m, 16 H), 6.28 (s, 2 H), 7.06 (d, 4 H), 7.26 (d, 4 H), 7.42 (s, 2 H)
1b-167	0.49-1.10 (m, 26H), 1.10-1.77 (m, 26H), 1.83-2.11 (m, 1H), 2.63-3.10 (m, 10H), 3.13-3.27 (m, 2H), 3.33-3.47 (m, 1H), 4.05-4.20 (m, 2H), 4.32-4.61 (m, 2H), 4.77-5.76 (m, 11H), 6.97-7.36 (m, 8H), 7.37-7.78 (m, 4H)
1b-168	0.67-0.95 (m, 26 H), 1.18-1.74 (m, 16 H), 2.06 (s, 6 H), 2.68-3.07 (m, 16 H), 3.80 (s, 6 H), 4.39-5.72 (m, 14 H), 7.04 (d, 4 H), 7.23-7.27 (m, 4 H)
1b-169	0.67-0.95 (m, 26 H), 1.09-1.75 (m, 28 H), 2.42 (q, 4 H), 2.68-3.09 (m, 16 H), 4.07 (q, 4 H), 4.39-5.72 (m, 14 H), 7.05 (d, 4 H), 7.25 (d, 4 H)
1b-170	0.55-0.95 (m, 34 H), 1.17-1.76 (m, 24 H), 2.68-3.07 (m, 16 H), 4.05 (q, 4 H), 4.39-5.72 (m, 14 H), 7.03 (d, 4 H), 7.24-7.27 (m, 4 H)
1b-171	0.65 - 1.05 (m, 26 H) 1.18 - 1.76 (m, 22 H) 1.84 (br s, 12 H) 2.63 - 3.10 (m, 16 H) 3.82 - 3.96 (m, 3 H) 4.37 - 4.48 (m, 1 H) 4.97 - 5.76 (m, 11 H) 6.86 (m, 4 H) 7.15 - 7.32 (m, 6 H) 7.45 - 7.59 (m, 2 H)
1b-172	0.67 - 0.94 (m, 35 H), 1.21 - 1.94 (m, 21 H), 2.67 - 3.29 (m, 16 H), 3.55 - 3.57 (m, 4 H), 4.40 - 4.50 (m, 1 H), 5.07 - 5.69 (m, 11 H), 7.13 (d, J = 7.8 Hz, 4 H), 7.19 (s, 2 H), 7.27 (d, J = 7.5 Hz, 4 H), 7.47 - 7.48 (m, 2 H)
1b-173	0.63-0.92 (m, 26 H), 1.13-1.71 (m, 16 H), 2.66-3.02 (m, 16 H), 4.36-5.67 (m, 8 H), 5.91 (s, 4 H), 6.86-6.88 (m, 2 H), 6.98 (d, 4 H), 7.15-7.19 (m, 4 H), 7.33-7.37 (m, 2 H), 7.57 (s, 2 H), 7.77 (d, 2 H), 7.84-7.89 (m, 2 H), 8.62 (d, 2 H)
1b-174	0.68 - 0.93 (m, 28 H), 1.23 - 1.83 (m, 14 H), 2.65 - 3.18 (m, 16 H), 4.40 - 4.50 (m, 1 H), 5.01 - 5.72 (m, 11 H), 7.17 - 7.19 (m, 6 H), 7.25-7.27 (m, 2 H), 7.28-7.31 (m, 4 H), 7.63 (s, 2 H), 8.10-8.13 (m, 2H)
1b-175	0.66 - 0.94 (m, 26 H), 1.20 - 1.80 (m, 16 H), 2.66 - 3.31 (m, 16 H), 4.40 - 4.50 (m, 1 H), 5.01 - 5.69 (m, 11 H), 6.98 (d, J = 8.3 Hz, 2H), 7.10 (t, J = 6.1 Hz, 2H), 7.20 (d, J = 7.7 Hz, 4 H), 7.29 (d, J = 7.8 Hz, 4 H), 7.47 (s, 2 H), 7.81 (t, J = 7.2 Hz, 2 H), 7.93 (d, J = 5.2 Hz, 2 H), 8.15 (s, 2 H)
1b-176	0.67-0.95 (m, 26 H), 1.06 (t, 6 H), 1.18-1.76 (m, 16 H), 2.67-3.07 (m, 16 H), 3.40 (q, 4 H), 4.39-5.70 (m, 16 H), 6.27 (s, 2 H), 7.07 (d, 4 H), 7.25 (d, 4 H), 7.40 (s, 2 H)
1b-177	0.63-0.92 (m, 26 H), 1.13-1.70 (m, 16 H), 2.50 (s, 6 H), 2.66-3.02 (m, 16 H), 4.36-5.67 (m, 8 H), 5.91 (s, 4 H), 6.83 (s, 2 H), 7.03 (d, 4 H), 7.17-7.21 (m, 6 H), 7.54-7.58 (m, 4 H), 7.72-7.77 (m, 2 H)
1b-178	0.66-0.96 (m, 26 H), 1.14-1.76 (m, 22 H), 2.65-3.06 (m, 16 H), 4.19 (q, 4 H), 4.38-5.72 (m, 12 H), 6.21-6.23 (m, 2 H), 7.11-7.15 (m, 4 H), 7.26-7.29 (m, 6 H), 7.34-7.38 (m, 4 H), 7.73 (d, 4 H)

1b-179	0.67 - 0.94 (m, 27 H), 1.21 - 1.87 (m, 15 H), 2.32 - 3.06 (m, 24 H), 3.65 - 3.68 (m, 8 H), 4.40 - 4.50 (m, 1 H), 5.01 - 5.71 (m, 11 H), 7.12 (d, J = 7.8 Hz, 4 H), 7.19 (s, 2 H), 7.26 (d, J = 7.7 Hz, 4 H), 7.31 - 7.32 (m, 2 H)
1b-180	0.66 - 0.94 (m, 26 H), 1.21 - 1.80 (m, 34 H), 2.67 - 3.21 (m, 16 H), 3.17 - 3.32 (m, 4 H), 3.76 (t, J = 5.5 Hz, 4 H), 4.40 - 4.50 (m, 1 H), 5.01 - 5.69 (m, 11 H), 6.93 - 6.96 (m, 2 H), 7.10 - 7.27 (m, 10 H), 7.49 (s, 2 H)
1b-181	0.49-0.53 (m, 4 H), 0.68-0.95 (m, 30 H), 1.20-1.78 (m, 18 H), 2.07 (s, 6 H), 2.67-3.06 (m, 16 H), 4.39-5.70 (m, 14 H), 7.06 (d, 4 H), 7.26 (d, 4 H)
1b-182	0.67 - 0.94 (m, 29 H), 1.21 - 1.83 (m, 21 H), 2.53 - 3.02 (m, 24 H), 4.40 - 4.50 (m, 1 H), 5.07 - 5.69 (m, 11 H), 7.00 (s, 2 H), 7.10 - 7.13 (m, 6 H), 7.24 - 7.26 (m, 4 H)
1b-183	0.70 - 0.94 (m, 28 H), 1.06 - 1.87 (m, 26 H), 2.67 - 3.02 (m, 24 H), 4.35 - 4.45 (m, 1 H), 5.13 - 5.69 (m, 11 H), 7.10 - 7.15 (m, 6 H), 7.24 - 7.27 (m, 6 H)
1b-184	0.70 - 0.94 (m, 25 H), 1.06 - 1.08 (m, 12 H), 1.21 - 1.87 (m, 17 H), 2.67 - 3.02 (m, 16 H), 3.56 – 3.60 (m, 2 H), 4.28 (s, 4 H), 4.40 - 4.50 (m, 1 H), 5.01 - 5.69 (m, 11 H), 7.14 - 7.16 (m, 4 H), 7.26 -7.28 (m, 4 H), 7.37 (s, 2 H), 7.68 (s, 2 H)
1b-185	0.87 - 0.94 (m, 27 H), 1.23 - 1.70 (m, 15 H), 2.68 - 2.13 (m, 20 H), 3.78 (bs, 4 H), 4.40 - 4.51 (m, 1 H), 5.08 - 5.71 (m, 11 H), 7.13 (d, J = 7.5 Hz, 4 H), 7.21 - 7.30 (m, 6 H), 7.60 (bs, 2 H), 8.04 (bs, 6 H)
1b-186	0.69-0.95 (m, 26 H), 1.05-1.14 (m, 6 H), 1.20-1.74 (m, 16 H), 2.11 (s, 6 H), 2.43-2.51 (m, 4 H), 2.67-3.06 (m, 16 H), 4.39-5.70 (m, 12 H), 5.87-5.89 (m, 2 H), 7.00 (d, 4 H), 7.25-7.28 (m, 4 H)
1b-187	0.69-0.95 (m, 26 H), 1.07 (t, 6 H), 1.20-1.74 (m, 16 H), 2.11 (s, 6 H), 2.43-2.52 (m, 4 H), 2.67-3.06 (m, 16 H), 4.39-5.70 (m, 12 H), 5.88 (s, 2 H), 7.00 (d, 4 H), 7.24-7.28 (m, 4 H)
1b-188	0.88 - 0.94 (m, 26 H), 1.16 - 1.53 (m, 28 H), 2.00 - 2.03 (m, 12 H), 2.68 - 3.01 (m, 16 H), 3.86 - 3.90 (m, 2 H), 4.40 - 4.50 (m, 1 H), 5.01 - 5.68 (m, 11 H), 6.97 (d, J = 7.7 Hz, 4 H), 7.25 (d, J = 7.8 Hz, 4 H)
1b-189	0.63-0.92 (m, 26 H), 1.14-1.71 (m, 16 H), 2.66-3.02 (m, 16 H), 4.36-5.67 (m, 8 H), 5.84 (s, 4 H), 6.86-6.88 (m, 2 H), 6.98 (d, 4 H), 7.16-7.19 (m, 4 H), 7.57 (s, 2 H), 7.79-7.89 (m, 4 H), 8.62-8.64 (m, 2 H)
1b-190	0.64-0.94 (m, 26 H), 1.16-1.72 (m, 16 H), 2.67-3.04 (m, 16 H), 3.86 (s, 6 H), 4.37-5.68 (m, 12 H), 6.48 (s, 2 H), 6.86-6.90 (m, 6 H), 7.20-7.25 (m, 4 H), 7.59 (s, 2 H), 7.70-7.75 (m, 2 H), 8.13-8.15 (m, 2 H)
1b-191	0.70 - 0.94 (m, 28 H), 1.15 - 1.87 (m, 20 H), 2.02 - 2.05 (m, 12 H), 2.67 - 3.31 (m, 16 H), 3.76 - 3.81 (m, 4 H), 4.40 - 4.50 (m, 1 H), 5.01 - 5.71 (m, 11 H), 6.98 - 7.00 (m, 4 H), 7.24 - 7.26 (m, 4 H)
1b-192	0.55 - 0.94 (m, 27 H), 1.14 - 1.87 (m, 15 H), 2.57 - 3.11 (m, 16 H), 3.35 - 3.55 (m, 12 H), 4.40 - 4.50 (m, 1 H), 4.83 - 5.71 (m, 11 H), 7.09 - 7.11 (m, 4 H), 7.34 - 7.36 (m, 4 H), 7.99 - 8.00 (m, 4 H)
1b-193	0.92 - 0.98 (m, 37 H), 1.23 - 1.70 (m, 17 H), 2.50 - 3.32 (m, 24 H), 4.40 - 4.51 (m, 1 H), 5.10 - 5.69 (m, 11 H), 7.07 - 7.11 (m, 6 H), 7.18 - 7.27 (m, 6 H)
1b-195	0.71 - 0.91 (m, 25 H), 1.23 - 1.74 (m, 17 H), 2.64 - 3.03 (m, 16 H), 4.40 - 4.45 (m, 1 H), 5.01 - 5.70 (m, 11 H), 6.90 (bs, 2 H), 7.24 - 7.31 (m, 8 H), 7.96 - 7.97 (m, 2 H), 8.52 - 8.53 (m, 2 H), 8.61 (bs, 2 H), 9.09 (s, 2 H)
1b-196	0.86 - 0.95 (m, 25 H), 1.29 - 1.74 (m, 17 H), 2.67 - 3.03 (m, 16 H), 4.40 - 4.45 (m, 1 H), 5.01 - 5.70 (m, 11 H), 6.59 (s, 2 H), 7.22 – 7.24 (m, 4 H), 7.30 - 7.38 (m, 8 H), 7.93 (s, 2 H)
1b-197	0.87 - 0.94 (m, 25 H), 1.21 - 1.28 (m, 12 H), 1.33 - 1.70 (m, 10 H), 1.99 (s, 6 H), 2.67 - 3.02 (m, 16 H), 3.85 - 3.91 (m, 4 H), 4.40 - 4.43 (m, 1 H), 5.01 - 5.68 (m, 12 H), 6.98 - 7.00 (m, 4 H), 7.25 - 7.27 (m, 6 H)
1b-198	0.90 - 0.94 (m, 25 H), 1.14 - 1.28 (m, 12 H), 1.34 - 1.70 (m, 10 H), 2.00 (s, 6 H), 2.67 - 3.03 (m, 16 H), 3.78 - 3.83 (m, 4 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.71 (m, 12 H), 7.11 - 7.13 (m, 4 H), 7.25 - 7.27 (m, 4 H), 7.39 - 7.42 (m, 2 H)
1b-199	0.67 - 0.94 (m, 26 H), 1.11 - 1.82 (m, 27 H), 2.13 (s, 6 H), 2.67 - 3.03 (m, 16 H), 3.98 - 4.04 (m, 2 H), 4.40 - 4.42 (m, 1 H), 5.03 - 5.69 (m, 12 H), 7.11 - 7.12 (m, 4 H), 7.26 - 7.27 (m, 4 H), 7.43 - 7.44 (m, 2 H)
1b-201	0.67 - 0.94 (m, 26 H), 1.23 - 1.81 (m, 16 H), 2.67 - 3.03 (m, 16 H), 3.34 (s, 6 H), 4.39 - 4.42 (m, 1 H), 4.90 (s, 4 H), 5.01 - 5.72 (m, 11 H), 7.14 - 7.53 (m, 12 H)

1b-202	0.67 - 0.96 (m, 26 H), 1.23 - 1.70 (m, 16 H), 2.68 - 3.07 (m, 16 H), 4.15 - 4.19 (m, 4 H), 4.35 - 4.45 (m, 1 H), 4.86 (s, 4 H), 5.01 - 5.74 (m, 11 H), 6.98 - 7.49 (m, 12 H), 12.21 - 12.34 (m, 2 H)
1b-203	0.68 - 0.94 (m, 26 H), 1.20 - 1.69 (m, 16 H), 2.67 - 3.03 (m, 16 H), 3.26 (6H, s), 3.55 - 3.57 (m, 4 H), 3.90 - 3.92 (m, 4 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.70 (m, 11 H), 7.12 - 7.50 (m, 12 H)
1b-205	0.69-0.98 (m, 32 H), 1.18-1.76 (m, 20 H), 2.45-2.51 (m, 4 H), 2.67-3.07 (m, 16 H), 4.39-5.70 (m, 12 H), 6.09 (s, 2 H), 7.00 (d, 4 H), 7.24-7.28 (m, 4 H), 7.38 (s, 2 H)
1b-206	0.07-0.10 (m, 4 H), 0.42-0.47 (m, 4 H), 0.68-0.95 (m, 28 H), 1.19-1.75 (m, 16 H), 2.41-2.45 (m, 4 H), 2.67-3.06 (m, 16 H), 4.39-5.70 (m, 12 H), 6.20 (s, 2 H), 6.99 (d, 4 H), 7.24-7.28 (m, 4 H), 7.38 (s, 2 H)
1b-207	0.65-0.95 (m, 26 H), 1.18-1.75 (m, 16 H), 2.63-3.06 (m, 22 H), 4.38-5.67 (m, 12 H), 6.67 (s, 2 H), 6.90 (d, 4 H), 7.22-7.26 (m, 4 H), 7.67 (s, 2 H), 8.67-8.70 (m, 4 H)
1b-208	0.63-0.91 (m, 26 H), 1.14-1.70 (m, 16 H), 2.66-3.03 (m, 16 H), 4.36-5.67 (m, 8 H), 5.86 (s, 4 H), 7.00 (d, 4 H), 7.10 (s, 2 H), 7.17-7.21 (m, 4 H), 7.65 (s, 2 H), 8.58 (s, 2 H), 8.67 (s, 2 H), 9.08 (s, 2 H)
1b-209	0.69-0.95 (m, 38 H), 1.20-1.80 (m, 18 H), 2.41 (d, 4 H), 2.67-3.06 (m, 16 H), 4.39-5.69 (m, 12 H), 6.08 (s, 2 H), 7.00 (d, 4 H), 7.24-7.28 (m, 4 H), 7.39 (s, 2 H)
1b-210	0.68-1.03 (m, 38 H), 1.22-1.76 (m, 20 H), 2.66-3.06 (m, 18 H), 4.38-5.69 (m, 12 H), 6.09 (s, 2 H), 7.01 (d, 4 H), 7.24-7.28 (m, 4 H), 7.39 (s, 2 H)
1b-211	0.68-0.96 (m, 26 H), 1.21-1.76 (m, 16 H), 2.67-3.06 (m, 16 H), 4.39-5.70 (m, 12 H), 6.85 (s, 2 H), 7.08 (d, 4 H), 7.17-7.44 (m, 6 H), 7.59 (s, 2 H)
1b-212	0.70-0.97 (m, 26 H), 1.20-1.75 (m, 22 H), 2.67-3.06 (m, 22 H), 4.39-5.69 (m, 14 H), 6.24 (s, 2 H), 7.05 (d, 4 H), 7.26 (d, 4 H), 7.43 (s, 2 H)
1b-213	0.68-0.96 (m, 26 H), 1.20-1.76 (m, 26 H), 1.87-1.95 (m, 4 H), 2.66-3.05 (m, 16 H), 3.37-3.55 (m, 8 H), 4.39-5.66 (m, 12 H), 6.16 (s, 2 H), 6.90 (d, 4 H), 7.24 (d, 4 H), 7.45 (s, 2 H)
1b-214	0.67-1.09 (m, 38 H), 1.18-1.75 (m, 16 H), 2.64-3.09 (m, 26 H), 4.39-5.69 (m, 12 H), 6.13 (s, 2 H), 6.98 (d, 4 H), 7.24 (d, 4 H), 7.38 (s, 2 H)
1b-215	0.68-1.00 (m, 30 H), 1.17-1.75 (m, 20 H), 2.67-3.07 (m, 16 H), 4.38-5.70 (m, 12 H), 6.43 (s, 2 H), 7.08 (d, 4 H), 7.26 (d, 4 H), 7.48 (s, 2 H)
1b-216	0.69-0.98 (m, 26 H), 1.20-1.82 (m, 18 H), 1.98-2.09 (m, 2 H), 2.67-3.06 (m, 18 H), 4.39-5.70 (m, 12 H), 6.18 (s, 2 H), 7.05-7.10 (m, 4 H), 7.27 (d, 4 H), 7.42 (s, 2 H)
1b-217	0.68-1.01 (m, 26 H), 1.15-1.75 (m, 24 H), 2.66-3.08 (m, 16 H), 4.38-5.71 (m, 12 H), 6.37 (s, 2 H), 7.09 (d, 4 H), 7.25-7.30 (m, 4 H), 7.43 (s, 2H)
1b-218	0.67 - 0.95 (m, 32 H), 1.00 (br s, 1 H), 1.07 (br s, 1 H), 1.17 - 1.32 (m, 9 H), 1.33 - 1.48 (m, 4 H), 1.48 - 1.75 (m, 5 H), 2.67 (s, 2 H), 2.75 (br d, 4 H), 2.82 - 2.94 (m, 6 H), 3.03 (br d, 3 H), 4.41 (br d, 1 H), 4.78 - 5.07 (m, 2 H), 5.07 - 5.26 (m, 4 H), 5.34 (q, 1 H), 5.42 - 5.55 (m, 5 H), 5.56 - 5.75 (m, 1 H), 6.19 (s, 2 H), 7.04 (br d, 4 H), 7.26 (br d, 4 H), 7.37 (s, 2 H)
1b-219	0.65 - 0.90 (m, 32 H), 0.94 (br d, 2 H), 1.14 (s, 5 H), 1.22 - 1.31 (m, 5 H), 1.32 - 1.39 (m, 2 H), 1.40 - 1.57 (m, 4 H), 1.57 - 1.78 (m, 3 H), 2.67 (s, 2 H), 2.75 (d, 4 H), 2.81 - 2.94 (m, 6 H), 2.97 - 3.10 (m, 3 H), 3.33 (s, 8 H), 5.03 (q, 1 H), 5.08 - 5.26 (m, 3 H), 5.31 - 5.51 (m, 5 H), 5.56 - 5.71 (m, 1 H), 6.08 (s, 2 H), 7.02 (br d, 3 H), 7.27 (br dd, 3 H), 7.36 (s, 2 H)
1b-220	0.69 - 0.96 (m, 32 H), 1.21 – 1.74 (m, 9 H), 1.47 - 1.74 (m, 6 H), 2.65 - 2.85 (m, 9 H), 2.85 - 2.92 (m, 11 H), 3.03 (br d, 3 H), 3.35 (s, 10 H), 4.41 (br d, 1 H), 5.03 (q, 1 H), 5.12 (br d, 3 H), 5.18 - 5.38 (m, 2 H), 5.41 - 5.55 (m, 5 H), 5.58 - 5.73 (m, 1 H), 6.23 (s, 2 H), 7.02 (br d, 4 H), 7.26 (br dd, 4 H), 7.44 (s, 2 H)
1b-221	0.69 - 0.95 (m, 32 H), 0.98 - 1.75 (m, 8 H), 2.66 (s, 2 H), 2.69 - 2.79 (m,4 H), 2.81 - 2.93 (m, 6 H), 2.96 - 3.10 (m, 3 H), 3.32 (s, 8 H), 4.38 - 4.50 (m, 4 H), 4.63 - 4.71 (m, 4 H), 4.92 - 5.07 (m, 1 H), 5.08 - 5.15 (m, 7 H), 5.17 - 5.36 (m, 2 H), 5.39 - 5.52 (m, 2 H), 5.57 - 5.71 (m, 1 H), 6.14 (s, 2 H), 7.00 (m, 4 H), 7.27 (m,4H), 7.45 (s,2 H)
1b-222	0.55 - 1.01 (m, 38 H), 1.08 (br d, 1 H), 1.20 - 1.31 (m, 6 H), 1.35 - 1.62 (m, 8 H), 1.65 - 1.73 (m, 2 H), 2.67 (s, 2 H), 2.76 (br d, 4 H), 2.82 - 2.94 (m, 6 H), 3.02 (br s, 3 H), 3.31 (s, 4 H), 4.38 - 4.45 (m, 1 H), 4.96 - 5.17 (m, 3 H), 5.19 - 5.26 (m, 1 H), 5.29 - 5.51 (m, 6 H), 5.60 - 5.71 (m, 1 H), 5.86 (s, 2 H), 6.99 - 7.13 (m, 4 H), 7.21 - 7.35 (m, 4 H)

1b-223	0.67-0.94 (m, 26H), 1.26-2.11 (m, 24H), 2.67-3.01 (m, 16H), 3.70-3.82 (m, 4H), 4.35-4.45 (m, 1H), 4.86-4.88 (m, 2H), 5.08-5.67 (m, 11H), 6.24 (s, 2H), 7.03-7.25 (m, 8H), 7.39 (s, 2H)
1b-224	0.67-0.94 (m, 26H), 1.26-1.71 (m, 16H), 2.67-3.02 (m, 24H), 3.38-3.40 (m, 2H), 4.35-4.45 (m, 1H), 5.10-5.63 (m, 11H), 6.32 (s, 2H), 7.00-7.27 (m, 8H), 7.42 (s, 2H)
1b-225	0.67-0.94 (m, 26H), 1.26-1.77 (m, 20H), 2.22-2.26 (m, 8H), 2.65-3.02 (m, 22H), 4.40-4.43 (m, 1H), 5.10-5.67 (m, 11H), 6.41 (s, 2H), 7.04-7.25 (m, 8H), 7.46 (s, 2H)
1b-226	0.67-0.94 (m, 26H), 1.26-1.77 (m, 16H), 2.65-3.02 (m, 16H), 4.40-4.43 (m, 1H), 5.08-5.67 (m, 15H), 6.41 (s, 2H), 6.90-7.28 (m, 18H), 7.46 (s, 2H)
1b-227	0.67-0.94 (m, 26H), 1.26-1.77 (m, 16H), 2.65-3.08 (m, 24H), 4.40-4.43 (m, 1H), 4.55-4.60 (m, 2H), 5.08-5.67 (m, 11H), 6.45 (s, 2H), 6.98-7.27 (m, 8H), 7.43 (s, 2H)
1b-228	0.67-1.06 (m, 38H), 1.26-1.77(m,16H), 2.65-3.02(m,16H), 3.55-3.58(m,2H), 4.41 (s,5H), 5.08-5.67(m,11H), 6.26 (s,2H), 7.05-7.07(m,4H), 7.24-7.27(m,4H), 7.39 (s,2H)
1b-229	0.67-0.94 (m, 26H), 1.26-2.05 (m, 32H), 2.65-3.02 (m, 22H), 4.40-4.42 (m, 1H), 5.08-5.67 (m, 11H), 6.28 (s, 2H), 7.00-7.02 (m, 4H), 7.23-7.25 (m, 4H), 7.43 (s, 2H)
1b-230	0.67-0.94 (m, 26H), 1.07 (s, 12H), 1.26-1.73 (m, 16H), 2.65-3.02 (m, 20H), 4.40-4.42 (m, 1H), 4.52 (s, 2H), 5.08-5.67 (m, 11H), 6.12 (s, 2H), 6.97-6.99 (m, 4H), 7.25-7.27 (m, 4H), 7.37 (s, 2H)
1b-231	0.69-1.00 (m, 26 H), 1.20-1.81 (m, 18 H), 2.06-2.16 (m, 2 H), 2.66-3.07 (m, 16 H), 3.31-3.49 (m, 6 H), 3.67-3.84 (m, 4 H), 4.39-5.69 (m, 12 H), 6.18 (s, 2 H), 7.02 (d, 4 H), 7.25-7.29 (m, 4 H), 7.41 (s, 2 H)
1b-232	0.64-0.93 (m, 26 H), 1.14-1.73 (m, 16 H), 2.66-3.04 (m, 16 H), 4.36-5.68 (m, 8 H), 5.86 (s, 4 H), 6.89 (s, 2 H), 7.03 (d, 4 H), 7.19-7.23 (m, 4 H), 7.60 (s, 2 H), 7.85 (d, 2 H), 7.93 (d, 2 H)
1b-233	0.66-0.94 (m, 26 H), 1.18-1.70 (m, 16 H), 2.29 (s, 6 H), 2.66-3.04 (m, 16 H), 4.37-5.68 (m, 12 H), 6.16 (s, 2 H), 6.48-6.54 (m, 4 H), 7.00 (d, 4 H), 7.23-7.27 (m, 4 H), 7.53 (s, 2H)
1b-234	0.54 - 1.78 (m, 62 H), 2.66 - 3.32 (m, 16 H), 5.07 - 5.94 (m, 12 H), 7.07 (m, 4 H), 7.23 - 7.32 (m, 5 H), 7.35 (s, 1 H)
1b-235	0.58 – 0.95 (m, 28 H), 1.12 – 1.70 (m, 24 H), 2.24 (br d, 2 H), 2.44 - 2.49 (m, 1 H), 2.65 - 2.70 (m, 1 H), 2.77 - 3.04 (m, 14 H), 3.31 (s, 6 H), 4.17 (s, 1 H), 5.01 – 5.67 (m, 9 H), 6.17 (s, 2 H), 7.10 (br d, 4 H), 7.30 (br d, 4 H), 7.41 (s, 2 H)

The following Formula (1A1-3) compounds described in Table 1c were prepared in accordance with the schemes and examples described herein.



(1A1-3)

The following Formula (1A1-3) compounds described in Table 1c were prepared in accordance with the schemes and examples described herein. Examples 1c-1, 1c-2, and 1c-3 are examples wherein R^c and R^d are each alkyl and wherein the alkyls join together to form a cycloalkyl ring (e.g., cyclobutyl); and wherein $R^{c'}$ and $R^{d'}$ are each alkyl and wherein the alkyls join together to form a cycloalkyl ring (e.g., cyclobutyl).

Table 1c. Compounds of Formula (1A1-3).

#	3 and 3'	4 and 4'	5 and 5'	R^c and R^d	$R^{c'}$ and $R^{d'}$
1c-1	H	H	H		
1c-2	H	Cl	H		
1c-3	H	isopropoxy	H		
				R^c and $R^{c'}$	R^d and $R^{d'}$
1c-4	H	H	H	H	
1c-5	H	isopropoxy	H	H	
1c-6	H	H	H	methyl	methyl
1c-7	H	$-NO_2$	H	methyl	methyl
1c-8	H		H	methyl	methyl
1c-9	H	methyl	H	methyl	methyl
1c-10	H	isopropoxy	H	methyl	methyl
1c-11	H	Br	H	methyl	methyl
1c-12	$-NO_2$	H	H	methyl	methyl
1c-13	$-CF_3$	H	$-CF_3$	H	methyl

The following Formula (1A1-3) compounds and example #'s refer to those compounds depicted in Table 1c. In one aspect of the invention, are Formula (1A1-3) compounds selected from the group consisting of:

(1c-1). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(1-(1H-pyrazol-1-yl)cyclobutyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1190);
(1c-2). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(1-(4-chloro-1H-pyrazol-1-yl)cyclobutyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1258);
(1c-3). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-(1-(4-isopropoxy-1H-pyrazol-1-yl)cyclobutyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1306);
(1c-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(cyclopropyl(1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1190);
(1c-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(cyclopropyl(4-isopropoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1306);
(1c-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(2-(1H-pyrazol-1-yl)propan-2-yl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);
(1c-7). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-(2-(4-nitro-1H-pyrazol-1-yl)propan-2-yl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1255);
(1c-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(2-(4-cyclopropyl-1H-pyrazol-1-yl)propan-2-yl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1246);
(1c-9). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-(2-(4-methyl-1H-pyrazol-1-yl)propan-2-yl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(1c-10). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-(2-(4-isopropoxy-1H-pyrazol-1-yl)propan-2-yl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1282);

(1c-11). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(2-(4-bromo-1H-pyrazol-1-yl)propan-2-yl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1323);

(1c-12). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-(2-(3-nitro-1H-pyrazol-1-yl)propan-2-yl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1255); and

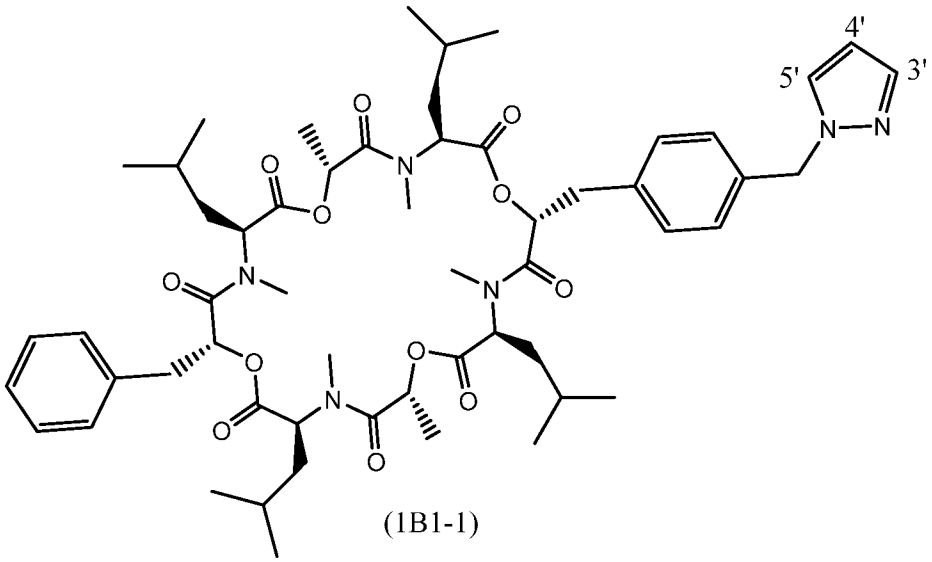
(1c-13). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((R)-1-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)ethyl)benzyl)-18-(4-((S)-1-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)ethyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1409).

Table 1c'. Formula (1A1-3) Compound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

Example	NMR
1c-1	0.65 - 1.06 (m, 26 H) 1.15 - 2.03 (m, 20 H) 2.62 - 3.11 (m, 24 H) 4.37 - 4.46 (m, 1 H) 4.99 - 5.75 (m, 7 H) 6.21 - 6.30 (m, 2 H) 7.09 - 7.20 (m, 4 H) 7.23 - 7.34 (m, 4 H) 7.44 - 7.52 (m, 2 H) 7.64 - 7.75 (m, 2 H)
1c-3	0.61-1.07 (m, 26H), 1.12-1.77 (m, 27H), 1.78-2.05 (m, 4H), 2.59-3.17 (m, 23H), 4.08-4.23 (m, 2H), 4.35-4.51 (m, 1H), 4.99-5.77 (m, 10H), 7.03-7.18 (m, 4H), 7.18-7.33 (m, 6H), 7.35-7.54 (m, 2H)
1c-4	0.29 - 0.52 (m, 4 H) 0.52 - 0.98 (m, 28 H) 1.14 - 1.82 (m, 20H) 2.63 - 3.12 (m, 16 H) 4.35 - 4.50 (m, 1 H) 4.63 - 4.72 (m, 2 H) 4.98 - 5.76 (m, 7 H) 6.22 - 6.29 (m, 2 H) 7.18 - 7.32 (m, 8 H) 7.39 - 7.46 (m, 2 H) 7.85 - 7.94 (m, 2 H)
1c-5	0.28 - 1.80 (m, 64 H) 2.63 - 2.98 (m, 16 H) 4.07 - 4.20 (m, 2 H) 4.36 - 4.46 (m, 1 H) 4.46 - 4.55 (m, 2 H) 4.99 - 5.74 (m, 7 H) 7.15 (s, 2 H) 7.17 - 7.30 (m, 8 H) 7.56 - 7.63 (m, 2 H)
1c-6	0.60 - 1.07 (m, 26 H) 1.16 - 1.77 (m, 16 H) 1.82 - 1.96 (m, 12 H) 2.63 - 3.09 (m, 16 H) 4.36 - 4.46 (m, 1 H) 4.97 - 5.72 (m, 7 H) 6.26 - 6.36 (m, 2 H) 6.79 - 6.90 (m, 4 H) 7.20 (br d, J=7.82 Hz, 4 H) 7.45 - 7.53 (m, 2 H) 7.76 - 7.86 (m, 2 H)
1c-7	0.61 - 1.10 (m, 26 H) 1.12 - 1.75 (m, 16 H) 1.95 (s, 12 H) 2.63 - 3.10 (m, 16 H) 4.36 - 4.50 (m, 1 H) 4.97 - 5.74 (m, 7 H) 7.02 - 7.10 (m, 4 H) 7.22 - 7.32 (m, 4 H) 8.24 - 8.34 (m, 2 H) 8.92 - 9.02 (m, 2 H)
1c-9	0.62 - 1.08 (m, 26 H) 1.17 - 1.76 (m, 16 H) 1.79 - 1.92 (m, 12 H) 2.02 (s, 6 H) 2.65 - 3.09 (m, 16 H) 4.38 - 4.46 (m, 1 H) 4.97 - 5.73 (m, 7 H) 6.83 - 6.93 (m, 4 H) 7.16 - 7.25 (m, 4 H) 7.26 - 7.34 (m, 2 H) 7.51 - 7.58 (m, 2 H)
1c-10	0.66 - 1.07 (m, 26 H) 1.14 - 1.77 (m, 28 H) 1.80 - 1.90 (m, 12 H) 2.64 - 3.07 (m, 16 H) 4.12 - 4.24 (m, 2 H) 4.38 - 4.47 (m, 1 H) 4.98 - 5.73 (m, 7 H) 6.81 - 6.90 (m, 4 H) 7.17 - 7.26 (m, 6 H) 7.48 - 7.54 (m, 2 H)
1c-11	0.70 - 0.94 (m, 26 H), 1.23 - 1.89 (m, 16 H), 2.32 - 2.42 (m, 12 H), 2.45 - 3.31 (m, 16 H), 4.40 - 4.50 (m, 1 H), 5.10 - 5.68 (m, 7 H), 6.90 - 6.93 (m, 4 H), 7.22 - 7.24 (m, 4 H), 7.58 - 7.59 (m, 2 H), 8.06 - 8.08 (m, 2 H)
1c-12	0.62 - 1.09 (m, 28 H) 1.13 - 1.77 (m, 17 H) 1.96 (s, 12 H) 2.63 - 2.98 (m, 13 H) 4.35 - 4.48 (m, 1 H) 4.96 - 5.79 (m, 7 H) 7.03 (br d, J=7.58 Hz, 4 H) 7.08 - 7.17 (m, 2 H) 7.28 (br d, J=7.83 Hz, 4 H) 8.11 - 8.24 (m, 2 H)
1c-13	0.70 - 0.90 (m, 25 H), 1.23 - 1.59 (m, 17H), 1.83 (s, 6 H), 2.65 - 3.18 (m, 16 H), 4.40 - 4.50 (m, 1 H), 5.02 - 5.84 (m, 9 H), 7.16 - 7.30 (m, 8 H), 7.59 (s, 2 H)

The following compound (mass; NMR): (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(2-(3,5-dimethyl-1H-1,2,4-triazol-1-yl)propan-2-yl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1224; 1H NMR (400 MHz, DMSO-d6) δ ppm 0.69 - 1.00 (m, 26 H) 1.06 - 1.77 (m, 16 H) 1.81 - 1.94 (m, 18 H) 2.24 - 2.32 (m, 6 H) 2.65 - 3.14 (m, 16 H) 4.42 (br dd, J=10.88, 2.57 Hz, 1 H) 4.99 - 5.78 (m, 7 H) 7.08 - 7.16 (m, 4 H) 7.31 - 7.41 (m, 4 H)), was prepared similarly to those compounds of Table 1c, but for the replacement of the pyrazole moiety with a dimethyltriazole moiety.

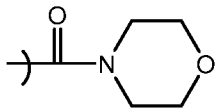
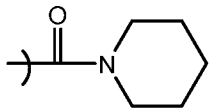
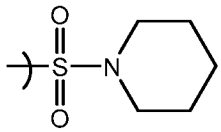
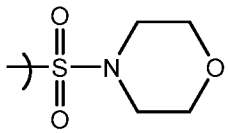
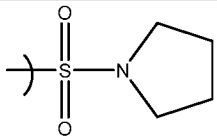
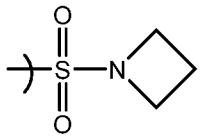
The following Formula (1B1-1) compounds (hybrid analogs) described in Table 2 were prepared in accordance with the schemes and examples described herein.

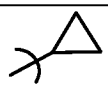
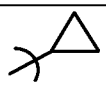
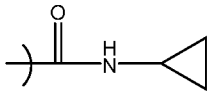
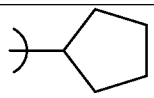
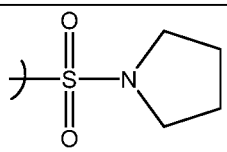
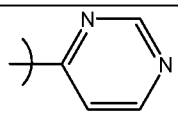
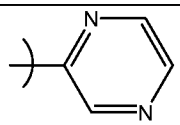
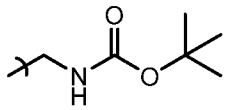


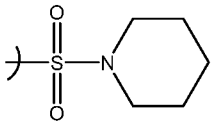
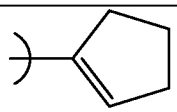
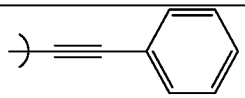
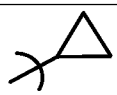
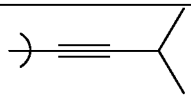
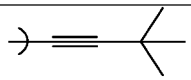
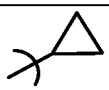
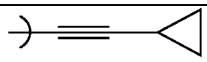
(1B1-1)

Table 2. Formula (1B1-1) Compounds

#	3’	4’	5’
2-1	H	H	H
2-2	H	methyl	H
2-3	H	phenyl	H
2-4	H	pyridin-4yl	H
2-5	H	4-F-phenyl	H
2-6	H	4-Cl-phenyl	H
2-7	methyl	H	methyl

2-8	H	t-butyl	H
2-9	H	ethyl	H
2-10	H	-CN	H
2-11	methyl	methyl	methyl
2-12	H	$-C(O)OCH_2CH_3$	H
2-13	H	$-C(O)CH_3$	H
2-14	H		H
2-15	H		H
2-16	methyl	Br	H
2-17	methyl	Br	methyl
2-18	H	$-CHF_2$	H
2-19	H	$-CH_2OH$	H
2-20	H	$-CF_3$	H
2-21	H		H
2-22	H	Br	H
2-23	H		H
2-24	H		H
2-25	H	Cl	H
2-26	H	propyl	H
2-27	H		H
2-28	H	F	H
2-29	H	$-NO_2$	H

2-30	H	-OH	H
2-31	H	-NHC(O)CH_3	H
2-32		H	
2-33	H	6-methyl-pyridin-3-yl	H
2-34	H		H
2-35	H	-CH_2CH_2OH	H
2-36	H	-NHS(O)$_2$$CH_3$	H
2-37	H	pyridin-3-yl	H
2-38	H		H
2-39	H	ethoxy	H
2-40	methyl		methyl
2-41	H	I	H
2-42	-CH_2OH	H	-CH_2OH
2-43	methyl	-NHC(O)CH_3	methyl
2-44	methyl	-OH	methyl
2-45	H		H
2-46	H		H
2-47	H	pyridin-2-yl	H
2-48	H		H
2-49	methyl	-S(O)$_2$$NH_2$	methyl
2-50	methyl	Cl	methyl
2-51	H	-C≡C	H
2-52	H	-CH_2NHC(O)CH_3	H

2-53	H	$-C(O)NH_2$	H
2-54	isopropyl	H	isopropyl
2-55	$-CF_3$	H	$-CF_3$
2-56	phenyl	H	H
2-57	Br	H	H
2-58	$-CF_3$	H	H
2-59	H	$-CH_2NH_2$	H
2-60	methyl		methyl
2-61	H		H
2-62	-CN	H	-CN
2-63	H	$-S(O)_2NH_2$	H
2-64	H		H
2-65	$-CH_2OH$	H	
2-66	H	H	
2-67	H	H	phenyl
2-68	H	H	t-butyl
2-69	H	H	isopropyl
2-70	H		H
2-71	H		H
2-72	t-butyl	H	H
2-73	methyl	$-NH_2$	methyl
2-74		H	H
2-75	H		H

2-76	H		H
2-77	H		H
2-78	methyl	-CN	methyl
2-79	methyl	F	methyl
2-80		$-NO_2$	
2-81	methyl	$-CF_3$	methyl
2-82	ethyl	$-NO_2$	ethyl
2-83	isopropyl	H	H
2-84	H		H
2-85		$-NH_2$	
2-86	ethyl	$-NH_2$	ethyl
2-87	$-NH_2$	H	H
2-88		H	H

The following Formula (1B1-1) compound names and example #s refer to those compounds depicted in Table 2. In one aspect of the invention, are Formula (1B1-1) compounds selected from the group consisting of:

(2-1). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-[[4-(pyrazol-1-ylmethyl)phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1030);

(2-2). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-[[4-[(4-methylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1043);

(2-3). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-[[4-[(4-phenylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1105);

(2-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(pyridin-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1106);

(2-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[[4-(4-fluorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1123);

(2-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[[4-(4-chlorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1139);

(2-7). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[(3,5-dimethylpyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1057);

(2-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[(4-tert-butylpyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1085);

(2-9). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[(4-ethylpyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1057);

(2-10). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-carbonitrile (1054);

(2-11). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((3,4,5-trimethyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1071);

(2-12). ethyl 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-

tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (1101);

(2-13). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-acetyl-1H-pyrazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1071);

(2-14). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(morpholine-4-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1142);

(2-15). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(piperidine-1-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1140);

(2-16). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-bromo-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1122);

(2-17). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-bromo-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1136);

(2-18). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1079);

(2-19). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1059)

(2-20). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1097)

(2-21). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(piperidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1176);
(2-22). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-bromo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1108);
(2-23). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(morpholinosulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1178);
(2-24). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(pyrrolidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1162);
(2-25). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-chloro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1064);
(2-26). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1071);
(2-27). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-(azetidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1148);
(2-28). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1047);
(2-29). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1074);

(2-30). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-hydroxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1045);
(2-31). N-(1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-4-yl)acetamide (1086);
(2-32). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1109);
(2-33). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(6-methylpyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1120);
(2-34). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-N-cyclopropyl-1H-pyrazole-4-carboxamide (1112);
(2-35). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(2-hydroxyethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1073);
(2-36). N-(1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-4-yl)methanesulfonamide (1122);
(2-37). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(pyridin-3-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1106);
(2-38). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1097);

(2-39). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-ethoxy-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-(hydroxymethyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1103);

(2-40). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-dimethyl-4-(pyrrolidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1190);

(2-41). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1155);

(2-42). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-bis(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1089);

(2-43). N-(1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-3,5-dimethyl-1H-pyrazol-4-yl)acetamide (1114);

(2-44). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-hydroxy-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1073);

(2-45). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(pyrimidin-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1107);

(2-46). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(pyrazin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1107);

(2-47). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1106);

(2-48). tert-butyl ((1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-4-yl)methyl)carbamate (1158);

(2-49). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-3,5-dimethyl-1H-pyrazole-4-sulfonamide (1136);

(2-50). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1092);

(2-51). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-ethynyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1053);

(2-52). N-((1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-4-yl)methyl)acetamide (1100);

(2-53). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide (1072);

(2-54). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-diisopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1113);

(2-55). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);

(2-56). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((3-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1105);

(2-57). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3-bromo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1108);

(2-58). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1097);

(2-59). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-(aminomethyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1058);

(2-60). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-dimethyl-4-(piperidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1205);

(2-61). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(cyclopent-1-en-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1095);

(2-62). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1079);

(2-63). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-sulfonamide (1108);

(2-64). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(phenylethynyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1129);
(2-65). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((5-cyclopropyl-3-(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1099);
(2-66). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((5-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1069);
(2-67). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((5-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1105);
(2-68). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((5-(tert-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1085);
(2-69). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-18-(4-((5-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1071);
(2-70). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(3-methylbut-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1095);
(2-71). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(3,3-dimethylbut-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1109);
(2-72). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3-(tert-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1085);

(2-73). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-amino-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1072);

(2-74). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1069);

(2-75). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(cyclopropylethynyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1093);

(2-76). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(prop-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1067);

(2-77). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(but-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1081);

(2-78). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-3,5-dimethyl-1H-pyrazole-4-carbonitrile (1082);

(2-79). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-fluoro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1075);

(2-80). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-dicyclopropyl-4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1154);

(2-81). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-dimethyl-4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-

4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1125);

(2-82). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3,5-diethyl-4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1130);

(2-83). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-18-(4-((3-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1071);

(2-84). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(1-methyl-1H-1,2,3-triazol-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1110);

(2-85). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-amino-3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1124);

(2-86). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((4-amino-3,5-diethyl-1H-pyrazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1100);

(2-87). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((3-amino-1H-pyrazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1044); and

(2-88). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((3-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1097).

Table 2'. Formula (1B1-1) Table 2 Compound NMR's (1H NMR (400Mhz, DMSO-d_6) δ ppm)

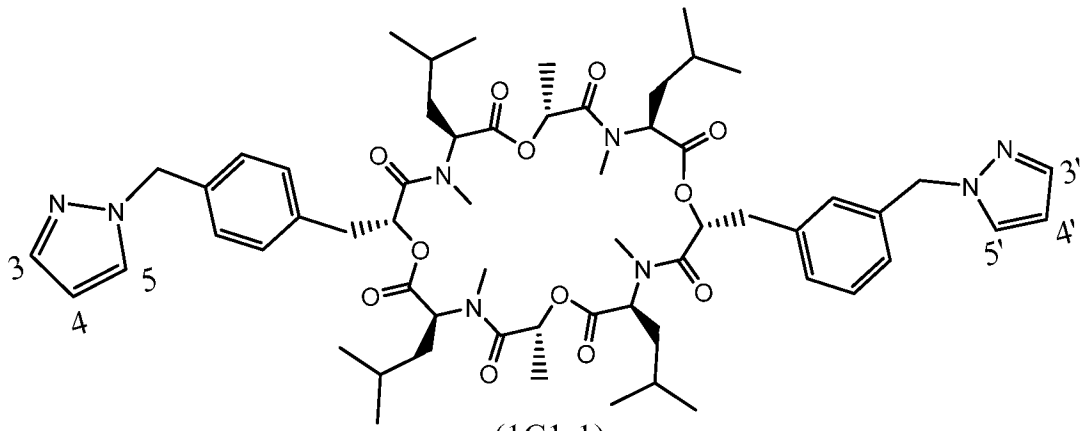
Example	NMR
2-1	0.67-0.96 (m, 26H), 1.17-1.76 (m, 16 H), 2.65-3.11 (m, 16 H), 4.38-5.75 (m, 10 H), 6.24-6.26 (m, 1 H), 7.14 (d, 2H) 7.22-7.33 (m, 7H), 7.42-7.45 (m, 1 H), 7.75-7.75 (m, 1H)
2-2	0.67-0.96 (m, 26H), 1.18-1.77 (m, 16 H), 1.98 (s, 3H), 2.65-3.11 (m, 16 H), 4.38-5.75 (m, 10 H), 7.13 (d, 2H) 7.22-7.34 (m, 8H), 7.47-7.49 (m, 1 H)
2-3	0.65-0.98 (m, 26H), 1.17-1.76 (m, 16 H), 2.66-3.12 (m, 16 H), 4.38-5.75 (m, 10 H), 7.16-7.36 (m, 12H), 7.54 (d, 2H), 7.89-7.91 (m, 1 H), 8.21-8.24 (m, 1H)
2-5	0.66-0.94 (m, 26H), 1.18-1.76 (m, 16 H), 2.66-3.11 (m, 16 H), 4.38-5.74 (m, 10 H), 7.15-7.36 (m, 11H), 7.55-7.60 (m, 2H), 7.86-7.89 (m, 1 H), 8.20-8.23 (m, 1H)
2-6	0.67-0.94 (m, 26H), 1.18-1.76 (m, 16 H), 2.65-3.11 (m, 16 H), 4.38-5.74 (m, 10 H), 7.21-7.40 (m, 11H), 7.58 (d, 2H), 7.90-7.92 (m, 1 H), 8.25-8.28 (m, 1H)
2-7	0.67-0.96 (m, 26H), 1.18-1.76 (m, 16 H), 2.08-2.13 (m, 6 H), 2.66-3.10 (m, 16 H), 4.38-5.74 (m, 10 H), 5.85 (s, 1 H), 7.01 (d, 2H) 7.22-7.33 (m, 7H)
2-8	0.67-0.96 (m, 26H), 1.17-1.76 (m, 25 H), 2.66-3.12 (m, 16 H), 4.39-5.75 (m, 10 H), 7.15 (d, 2H) 7.22-7.33 (m, 8H), 7.54-7.56 (m, 1 H)
2-9	0.65-0.96 (m, 26H), 1.11 (t, 3 H), 1.19-1.76 (m, 16 H), 2.40 (q, 2H), 2.66-3.12 (m, 16 H), 4.39-5.75 (m, 10 H), 7.14 (d, 2H) 7.23-7.33 (m, 8H), 7.50-7.53 (m, 1 H)
2-10	0.67-0.94 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.12 (m, 16 H), 4.39-5.75 (m, 10 H), 7.20-7.34 (m, 9 H), 8.05-8.07 (m, 1 H), 8.65-8.67 (m, 1H)
2-11	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 16 H), 1.84 (s, 3 H), 2.03-2.06 (m, 6 H), 2.67-3.11 (m, 16 H), 4.40-5.75 (m, 10 H), 7.01 (d, 2 H), 7.23-7.34 (m, 7 H)
2-12	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 19 H), 2.67-3.12 (m, 16 H), 4.19 (q, 2 H), 4.39-5.75 (m, 10 H), 7.22-7.34 (m, 9 H), 7.83-7.85 (m, 1 H), 8.39-8.40 (m, 1H)
2-13	0.67-0.96 (m, 26 H), 1.18-1.75 (m, 16 H), 2.34 (s, 3 H), 2.67-3.12 (m, 16 H), 4.39-5.75 (m, 10 H), 7.21-7.34 (m, 9 H), 7.91-7.93 (m, 1 H), 8.47-8.49 (m, 1H)
2-14	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.11 (m, 16 H), 3.55-3.62 (m, 8 H), 4.39-5.75 (m, 10 H), 7.21-7.35 (m, 9 H), 7.70-7.71 (m, 1 H), 8.19-8.21 (m, 1H)
2-15	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 22 H), 2.67-3.11 (m, 16 H), 3.49-3.55 (m, 4 H), 4.40-5.75 (m, 10 H), 7.19-7.33 (m, 9 H), 7.63-7.65 (m, 1 H), 8.11-8.13 (m, 1H)
2-16	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 16 H), 2.08 (s, 3 H), 2.67-3.11 (m, 16 H), 4.40-5.75 (m, 10 H), 7.19 (d, 2 H), 7.26-7.33 (m, 7 H), 7.92-7.94 (m, 1 H)
2-17	0.68-0.96 (m, 26 H), 1.18-1.76 (m, 16 H), 2.08-2.13 (m, 6 H), 2.67-3.10 (m, 16 H), 4.40-5.75 (m, 10 H), 7.06 (d, 2 H), 7.24-7.34 (m, 7 H)
2-18	0.67-0.96 (m, 26 H), 1.19-1.76 (m, 16 H), 2.67-3.10 (m, 16 H), 4.40-5.75 (m, 10 H), 6.99 (t, 1 H), 7.19-7.33 (m, 9 H), 7.67- 7.69 (m 1 H), 8.12-8.14 (m, 1 H)
2-19	0.68-0.96 (m, 26 H), 1.19-1.76 (m, 16 H), 2.66-3.10 (m, 16 H), 4.32 (s, 2 H), 4.40-5.75 (m, 10 H), 7.16 (d, 2 H), 7.22-7.35 (m, 8 H), 7.60- 7.63 (m, 1 H)
2-20	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.10 (m, 16 H), 4.40-5.73 (m, 10 H), 7.23-7.35 (m, 9 H), 7.87- 7.89 (m, 1 H), 8.46-8.48 (m ,1 H)
2-21	0.68-0.96 (m, 26 H), 1.18-1.76 (m, 22 H), 2.67-3.10 (m, 20 H), 4.40-5.73 (m, 10 H), 7.21-7.34 (m, 9 H), 7.77- 7.79 (m, 1 H), 8.44-8.45 (m ,1 H)
2-22	0.67-0.96 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.10 (m, 16 H), 4.40-5.75 (m, 10 H), 7.18-7.34 (m, 9 H), 7.53- 7.55 (m, 1 H), 8.01-8.03 (m ,1 H)
2-23	0.68-0.96 (m, 26 H), 1.19-1.76 (m, 16 H), 2.67-3.10 (m, 20 H), 3.64-3.67 (m, 4 H), 4.40-5.75 (m, 10 H), 7.23-7.34 (m, 9 H), 7.81- 7.83 (m, 1 H), 8.48-8.50 (m ,1 H)
2-24	0.67-0.96 (m, 26 H), 1.18-1.75 (m, 20 H), 2.67-3.12 (m, 20 H), 4.40-5.75 (m, 10 H), 7.19-7.34 (m, 9 H), 7.86 (s, 1 H), 8.50-8.52 (m, 1 H)
2-25	0.67-0.96 (m, 26 H), 1.17-1.75 (m, 16 H), 2.67-3.10 (m, 16 H), 4.41-5.75 (m, 10 H), 7.19-7.34 (m, 9 H), 7.53- 7.55 (m, 1 H), 8.03-8.05 (m ,1 H)
2-26	0.69 - 0.94 (m, 27 H), 1.23 - 1.70 (m, 18 H), 2.33 - 2.36 (m, 2 H), 2.67 - 3.05 (m, 16 H), 4.38 - 4.41 (m, 1 H), 5.10 - 5.70 (m, 11 H), 7.11 - 7.13 (m, 2 H), 7.25 -7.31 (m, 8 H), 7.51 (s,1H)

2-27	0.68-0.96 (m, 26 H), 1.18-1.75 (m, 16 H), 1.96-2.01 (m , 2 H), 2.67-3.07 (m, 16 H), 3.61-3.63 (m, 4 H), 4.40-5.75 (m, 10 H), 7.22-7.34 (m, 9 H), 7.92-7.94 (m, 1 H), 8.58-8.60 (m, 1 H)
2-28	0.76 - 0.94 (m, 24 H), 1.21 - 1.75 (m, 17 H), 2.67 - 3.05 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.03 - 5.73 (m, 10 H), 7.16 - 7.30 (m, 9 H), 7.46 (bs, 1 H), 7.91 (bs, 1 H)
2-29	0.66 - 0.96 (m, 24 H), 1.23 - 1.71 (m, 17 H), 2.67 - 3.06 (m, 16 H), 4.47 - 4.53 (m, 1 H), 5.08 - 5.73 (m, 10 H), 7.24 - 7.31 (m, 9 H), 8.26 (s, 1 H), 9.00 (s, 1 H)
2-30	0.77 - 0.95 (m, 24 H), 1.24 - 1.70 (m, 17 H), 2.68 - 3.04 (m, 16 H), 4.47 - 4.53 (m, 1 H), 5.02 - 5.71 (m, 10 H), 6.99 - 7.31 (m, 11 H), 8.39 (s, 1 H)
2-31	0.67 - 0.95 (m, 24 H), 1.23 - 1.70 (m, 17 H), 1.94 (s, 3 H), 2.67 - 3.06 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.08 - 5.35 (m, 10 H), 7.13 - 7.15 (m, 2 H), 7.24 - 7.31 (m, 8 H), 7.90 (s, 1 H), 9.91 (s, 1 H)
2-32	0.48 - 0.54 (m, 4 H), 0.67 - 0.94 (m, 24 H), 1.23 - 1.73 (m, 17 H), 2.67 - 3.06 (m, 18 H), 4.41-4.43 (m, 1H), 5.03-5.73 (m, 14 H), 7.03 - 7.05 (m, 2 H), 7.26 - 7.31 (m, 8 H)
2-34	0.45 - 0.47 (m, 2 H), 0.65 - 0.97 (m, 28 H), 1.23 - 1.70 (m, 17 H), 2.67 - 3.07 (m, 16 H), 4.38 - 4.42 (m, 1 H), 4.92 - 5.70 (m, 9 H), 7.18 - 7.31 (m, 9 H), 7.81 (s, 1 H), 8.00 - 8.01 (m, 1 H), 8.14 (s, 1 H)
2-35	0.65 - 0.98 (m, 24 H), 1.20 - 1.80 (m, 18 H), 2.65 - 3.15 (m, 16 H), 3.45 - 3.55 (m, 2 H), 4.40 - 4.45 (m, 1 H) 4.58 (t, *J* = 5.2 Hz, 1 H), 5.00 - 5.85 (m, 11 H), 7.10 - 7.30 (m, 10 H) 7.52 (s, 1 H)
2-36	0.65 - 1.00 (m, 24 H), 1.15 - 1.80 (m, 18 H), 2.65 - 3.15 (m, 19 H), 4.35 - 4.42 (m, 1 H), 5.00 - 5.80 (m, 9 H), 7.15 - 7.40 (m, 9 H), 7.69 (s, 2 H), 9.15 (s, 1 H)
2-37	0.66-0.95 (m, 26 H), 1.16-1.76 (m, 16 H), 2.64-3.09 (m, 16 H), 4.40-5.77 (m, 10 H), 7.23-7.42 (m, 7 H), 7.56-7.60 (m, 2 H), 8.12-8.15 (m, 1 H), 8.39 (s, 2 H), 8.80 (d, 1 H), 8.93-8.96 (m, 1 H), 9.58 (s, 1 H)
2-38	0.67-0.96 (m, 26 H), 1.18-1.75 (m, 22 H), 1.88-1.96 (m, 2 H), 2.67-3.10 (m, 17 H), 4.40-5.75 (m, 10 H), 7.12 (d, 2 H), 7.23-7.33 (m, 8 H), 7.52 (s, 1 H)
2-39	0.60 - 1.04 (m, 27 H) 1.16 - 1.78 (m, 18 H) 2.66 - 3.13 (m, 16 H) 3.84 (q, J= 6.97 Hz, 2 H) 4.35 - 4.49 (m, 3 H) 5.00 - 5.56 (m, 9 H) 5.64 - 5.76 (m, 1 H) 7.10 - 7.31 (m, 9 H) 7.44 - 7.51 (m, 1 H)
2-40	0.68-0.96 (m, 26 H), 1.18-1.77 (m, 20 H), 2.29 (s, 3 H), 2.39 (s, 3 H), 2.67-3.10 (m, 20 H), 4.40-5.75 (m, 10 H), 7.06 (d, 2 H), 7.23-7.33 (m, 7 H)
2-41	0.62 - 0.99 (m, 27 H), 1.14 - 1.82 (m, 15 H), 2.64 - 3.13 (m, 16 H), 4.37 - 4.49 (m, 1 H), 4.97 - 5.78 (m, 9 H), 7.19 (br d, 2 H), 7.22 - 7.36 (m, 7 H), 7.52 (s, 1 H), 7.94 - 7.99 (m, 1 H)
2-42	0.62 - 0.95 (m, 24 H), 1.15 - 1.75 (m, 18 H), 2.6 - 3.1 (m, 16 H), 4.32 - 4.39 (m, 4 H), 4.90 - 5.80 (m,12 H), 6.13 (s, 1 H), 7.05 - 7.15 (m, 2 H), 7.18 - 7.35 (m, 7 H)
2-43	0.68 - 0.95 (m, 24 H), 1.15 - 1.80 (m, 18 H), 1.95 - 2.01 (m, 9 H), 2.65 - 3.20 (m, 16 H), 4.38 - 4.48 (m, 1 H), 5.00 - 5.80 (m, 9 H), 7.00 - 7.08 (m, 2 H), 7.20 - 7.35 (m, 7 H), 8.90 (s, 1 H)
2-44	0.72 - 0.96 (m, 24 H), 1.17 - 1.70 (m, 17 H), 1.96 (s, 3 H), 2.00 (s, 3 H), 2.67 - 3.08 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 10 H), 6.95 - 6.97 (m, 2 H), 7.23 - 7.31 (m, 7 H), 7.55 (brs, 1 H)
2-45	0.69 - 0.95 (m, 24 H), 1.12 - 1.75 (m, 17 H), 2.65 - 3.05 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 10 H), 7.24 - 7.30 (m, 8 H), 7.71 - 7.73 (m, 2 H), 8.18 (s, 1 H), 8.57 - 8.58 (m, 1 H), 8.67 - 8.68 (m, 1 H), 9.03 (s, 1 H)
2-46	0.65 - 0.95 (m, 24 H), 1.12 - 1.78 (m, 17 H), 2.65 - 3.05 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 10 H), 7.26 - 7.30 (m, 8 H), 8.14 (s, 1 H), 8.40 (s, 2 H), 8.49 - 8.53 (m, 2 H), 8.96 (s, 1 H)
2-47	0.60 - 0.95 (m, 24 H), 1.10 - 1.70 (m, 17 H), 2.65 - 3.05 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 10 H), 7.15 - 7.31 (m, 10 H), 7.61 - 7.63 (m, 1 H), 7.70 - 7.80 (m, 1 H), 8.02 (s, 1 H), 8.34 (s, 1 H), 8.47 (s, 1 H)
2-48	0.67 - 0.96 (m, 24 H), 1.24 - 1.73 (m, 26 H), 2.68 - 3.06 (m, 16 H), 3.92 - 3.94 (m, 2 H), 4.37 - 4.48 (m, 1 H), 5.01 - 5.75 (m, 10 H), 7.11 -7.15 (m, 3 H), 7.25 - 7.31 (m, 8 H), 7.57 - 7.58 (m, 1 H)
2-49	0.68 - 0.96 (m, 24 H), 1.23 - 1.71 (m, 16 H), 2.27 (s, 3 H), 2.34 (s, 3 H), 2.67 - 3.06 (m, 16 H), 4.401 - 4.43 (m, 1 H), 5.01 - 5.73 (m, 11 H), 7.07 - 7.10 (m, 4 H), 7.24 - 7.31 (m, 7 H)

2-50	0.68 - 0.96 (m, 24 H), 1.23 - 1.73 (m, 16 H), 2.10 - 2.12 (m, 6 H), 2.67 - 3.06 (m, 16 H), 4.40-4.42 (m, 1H), 5.02-5.70 (m, 11 H), 7.05 - 7.06 (m, 2 H), 7.27 - 7.31 (m, 7 H)
2-51	0.72 - 0.94 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.67 - 3.04 (m, 16 H), 3.97 (s, 1 H), 4.40 - 4.43 (m, 1 H), 5.03 - 5.73 (m, 11 H), 7.17 - 7.30 (m, 9 H), 7.63 (s, 1 H), 8.09 - 8.10 (m, 1 H)
2-52	0.67 - 0.96 (m, 24 H), 1.23 - 1.70 (m, 17 H), 1.79 (s, 3 H), 2.68 - 3.06 (m, 16 H), 4.04 (d, *J* = 5.6 Hz, 2 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 10 H), 7.15 - 7.17 (m, 2 H), 7.26 - 7.33 (m, 8 H), 7.61 - 7.62 (m, 1 H), 8.05 - 8.15 (m, 1 H)
2-53	0.70 - 0.94 (m, 24 H), 1.12 - 1.80 (m, 17 H), 2.67 - 3.05 (m, 16 H), 4.35 - 4.48 (m, 1 H), 5.01 - 5.75 (m, 10 H), 6.97 (s, 1 H), 7.15 - 7.31 (m, 9 H), 7.52 (s, 1 H), 7.83 (s, 1 H), 8.14 (s, 1 H)
2-54	0.77 - 0.94 (m, 24 H), 1.05 - 1.71 (m, 30 H), 2.66 - 3.05 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.72 (m, 11 H), 5.92 (s, 1 H), 6.97 - 6.99 (m, 2 H), 7.24 - 7.31 (m, 7 H)
2-55	0.70 - 0.95 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.66 - 3.06 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.02 - 5.73 (m, 11 H), 7.11 - 7.13 (m, 2 H), 7.25 - 7.31 (m, 7 H), 7.63 (s, 1 H)
2-56	0.63 - 1.00 (m, 27 H), 1.11 - 1.82 (m, 15 H), 2.60 - 3.14 (m, 16 H), 4.37 - 4.49 (m, 1 H), 4.96 - 5.78 (m, 9 H), 6.69 – 6.75 (m, 1 H), 7.18 - 7.33 (m, 10 H), 7.34 - 7.42 (m, 2 H), 7.77 (d, 2 H), 7.81 - 7.87 (m, 1 H)
2-57	0.63 - 0.99 (m, 27 H), 1.14 - 1.79 (m, 15 H), 2.63 - 3.15 (m, 16 H), 4.38 - 4.46 (m, 1 H), 4.97 - 5.78 (m, 9 H), 6.35 -6.42 (m, 1 H), 7.16 – 7.22 (m, 2 H), 7.22 – 7.35 (m, 7 H), 7.81 - 7.88 (m, 1 H)
2-58	0.61 - 0.99 (m, 27 H), 1.14 - 1.80 (m, 15 H), 2.62 - 3.13 (m, 16 H), 4.37 - 4.46 (m, 1 H), 4.97-5.78 (m, 9H), 6.69 - 6.76 (m, 1 H), 7.18 - 7.36 (m, 9 H), 8.03 - 8.09 (m, 1 H)
2-59	0.69 - 0.95 (m, 24 H), 1.23 - 1.73 (m, 17 H), 2.67 - 3.05 (m, 16 H), 3.86 - 3.87 (m, 2 H), 4.41 - 4.43 (m, 1 H), 5.10 - 5.73 (m, 10 H), 7.17 - 7.31 (m, 9 H), 7.54 (s, 1 H), 7.85 (s, 1 H), 8.06 (brs, 3 H)
2-60	0.69-0.96 (m, 26 H), 1.19-1.76 (m, 22 H), 2.27 (s, 3 H), 2.36 (s, 3 H), 2.67-3.11 (m, 20 H), 4.39-5.75 (m, 10 H), 7.06 (d, 2 H), 7.22-7.34 (m, 7 H)
2-61	0.67-0.96 (m, 26 H), 1.19-1.76 (m, 16 H), 1.83-1.92 (m, 2 H), 2.36-2.51 (m, 4 H), 2.67-3.11 (m, 16 H), 4.40-5.76 (m, 10 H), 5.83 (s, 1 H), 7.16 (d, 2 H), 7.23-7.34 (m, 7 H), 7.57 (s, 1 H), 7.77-7.79 (m, 1 H)
2-62	0.70 - 0.95 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.66 - 3.07 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.12 - 5.73 (m, 11 H), 7.23 - 7.37 (m, 9 H), 7.99 (s, 1 H)
2-63	0.70 - 0.95 (m, 24 H), 1.24 - 1.72 (m, 16 H), 2.68 - 3.05 (m, 16 H), 4.39 - 4.43 (m, 1 H), 5.03 - 5.73 (m, 11 H), 7.25 - 7.30 (m, 11 H), 7.71 (s, 1 H), 8.26 (s, 1 H)
2-64	0.68 - 0.96 (m, 24 H), 1.24 - 1.70 (m, 16 H), 2.67 - 3.06 (m, 16 H), 4.36 - 4.40 (m, 1 H), 4.98 - 5.33 (m, 11 H), 7.20 - 7.46 (m, 14 H), 7.71 (s, 1 H), 8.15 - 8.17 (m, 1 H)
2-66	0.50-0.54 (m, 2 H), 0.68-0.96 (m, 28 H), 1.19-1.79 (m, 17 H), 2.67-3.10 (m, 16 H), 4.40-5.75 (m, 10 H), 5.90 (s, 1 H), 7.06 (d, 2 H) 7.23-7.34 (m, 8 H)
2-67	0.64-0.95 (m, 26 H), 1.19-1.76 (m, 16 H), 2.67-3.10 (m, 16 H), 4.39-5.75 (m, 10 H), 6.45 (s, 1 H), 6.90 (d, 2H) 7.21-7.46 (m, 12 H), 7.57 (s, 1 H)
2-68	0.69-0.96 (m, 26 H), 1.19-1.75 (m, 25 H), 2.66-3.10 (m, 16 H), 4.40-5.75 (m, 10 H), 6.09 (s, 1 H), 6.89 (d, 2 H) 7.22-7.37 (m, 8 H)
2-69	0.69-0.97 (m, 26 H), 1.07 (d, 6 H), 1.20-1.74 (m, 16 H), 2.66-3.10 (m, 17 H), 4.40-5.75 (m, 10 H), 6.11 (s, 1 H), 7.00 (d, 2 H) 7.23-7.38 (m, 8 H)
2-70	0.72 - 0.87 (m, 24 H), 1.14 - 1.70 (m, 22 H), 2.67 - 3.04 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.03 - 5.73 (m, 12 H), 7.15 - 7.17 (m, 2 H), 7.29 -7.31 (m, 7 H), 7.51 (brs, 1 H), 7.94 (brs, 1 H)
2-71	0.69 - 0.96 (m, 24 H), 1.23 - 1.70 (m, 24 H), 2.67 - 3.06 (m, 16 H), 4.40 - 4.43 (m, 1 H), 5.02 - 5.73 (m, 12 H), 7.15 - 7.17 (m, 2 H), 7.24 -7.31 (m, 7 H), 7.49 (brs, 1 H), 7.92 - 7.93 (m, 1 H)
2-72	0.67 - 0.96 (m, 24 H), 1.22 - 1.54 (m, 24 H), 2.67 - 3.06 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.01 - 5.75 (m, 12 H), 6.10 - 6.11 (m, 1 H), 7.10 -7.12 (m, 2 H), 7.25 - 7.31 (m, 7 H), 7.55 - 7.57 (m, 1 H)
2-74	0.70 - 0.96 (m, 28 H), 1.22 - 1.82 (m, 16 H), 2.67 - 3.06 (m, 16 H), 4.39 - 4.42 (m, 1 H), 5.09 - 5.92 (m, 12 H), 7.11 - 7.31 (m, 10 H), 7.57 (brs, 1 H)
2-75	0.63 - 0.94 (m, 28 H), 1.23 - 1.70 (m, 16 H), 2.67 - 3.04 (m, 16 H), 4.38 - 4.41 (m, 1 H), 5.03 - 5.70 (m, 12 H), 7.16 - 7.31 (m, 9 H), 7.50 (s, 1 H), 7.93 (s, 1 H)

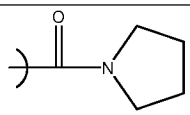
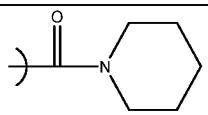
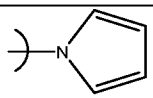
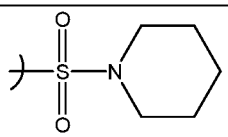
2-76	0.74 - 0.94 (m, 23 H), 1.23 - 1.70 (m, 19 H), 1.95 (s, 3H), 2.67 - 3.04 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.10 - 5.69 (m, 9 H), 7.16 (d, J = 7.6 Hz, 2 H), 7.29-7.31 (m, 7 H), 7.51 (s, 1 H), 7.94 – 7.96 (m, 1H)
2-77	0.69 - 0.98 (m, 24 H), 1.10 (t, J = 7.4 Hz, 3H), 1.23 - 1.69 (m, 18 H), 2.33 – 2.37 (m, 2 H), 2.67 - 3.31 (m, 16 H), 4.31 - 4.45 (m, 1 H), 5.1 - 5.8 (m, 9 H), 7.16 (d, J = 7.7 Hz, 2 H), 7.27 – 7.31 (m, 7 H), 7.51 (s, 1 H), 7.94 – 7.95 (m, 1 H)
2-78	0.67 - 0.95 (m, 26 H), 1.23 - 1.67 (m, 16 H), 2.21 (s, 3 H), 2.32 (s, 3 H), 2.67 - 3.37 (m, 16 H), 4.31 - 4.45 (m, 1 H), 5.08 - 5.8 (m, 9 H), 7.11 (d, J = 7.8 Hz, 2 H), 7.25 – 7.31 (m, 7 H)
2-79	0.68 - 0.95 (m, 24 H), 1.23 - 1.72 (m, 18 H), 2.07 – 2.09 (m, 6 H), 2.67 - 3.31 (m, 16 H), 4.31-4.45 (m, 1H), 5.03-5.73 (m, 9H), 7.03 (d, J=7.8 Hz, 2H), 7.25-7.31 (m, 7 H)
2-80	0.70 - 0.93 (m, 31 H), 1.06 - 1.27 (m, 10 H), 1.42 - 1.78 (m, 9 H), 2.33 - 2.45 (m, 2 H), 2.67 - 3.05 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.02 - 5.70 (m, 9 H), 7.08 - 7.09 (m, 2 H), 7.28 - 7.30 (m, 7 H)
2-81	0.86 - 0.95 (m, 26 H), 1.27 - 1.70 (m, 16 H), 2.20 (s, 3H), 2.27 (s, 3 H), 2.67 - 3.31 (m, 16 H), 4.40 - 4.45 (m, 1 H), 5.10 - 5.69 (m, 9 H), 7.08 – 7.09 (m, 2 H), 7.25 - 7.30 (m, 7 H)
2-82	0.79 - 0.96 (m, 28 H), 1.17 - 1.71 (m, 20 H), 2.66 – 3.05 (m, 20 H), 4.39 - 4.42 (m, 1 H), 5.11 - 5.73 (m, 9 H), 7.15 - 7.17 (m, 2 H), 7.25 - 7.31 (m, 7 H)
2-83	0.70 - 0.94 (m, 26 H), 1.06 - 1.7 (m, 22 H), 2.67 - 3.15 (m, 17 H), 4.35 - 4.45 (m, 1 H), 5.02 - 5.71 (m, 9 H), 6.06 – 6.07 (m, 1 H), 7.12 (d, J = 7.1 Hz, 2 H), 7.25 – 7.3 (m, 7 H), 7.59 (s, 1 H)
2-84	0.65 - 0.94 (m, 26 H), 1.22 - 1.70 (m, 16 H), 2.67 - 3.05 (m, 16 H), 4.03 (s, 3 H), 4.35 - 4.45 (m, 1 H), 5.02 - 5.72 (m, 9 H), 7.23 - 7.31 (m, 9 H), 7.76 (s, 1 H), 8.09 - 8.14 (m, 2 H)
2-85	0.54 - 0.94 (m, 32 H), 1.20 - 1.73 (m, 18 H), 2.67 - 3.05 (m, 16 H), 4.40 - 4.43 (m, 1 H), 5.04 - 5.70 (m, 13 H), 6.92 - 7.31 (m, 9 H)
2-86	0.65 - 0.94 (m, 29 H), 1.11 (t, J = 7.2 Hz, 3 H), 1.24 - 1.70 (m, 16 H), 2.42 - 2.44 (m, 4H), 2.67-3.06 (m, 16H), 4.35-4.45 (m,1H), 5.01-5.75 (m, 11 H), 6.95 - 7.31 (m, 9 H)
2-87	0.68 - 0.98 (m, 26 H), 1.20 - 1.78 (m, 16 H), 2.64 - 3.13 (m, 16 H), 4.39 - 4.43 (m, 1 H), 4.51 (bs, 2 H), 4.96 - 5.74 (m, 9 H), 7.08 - 7.39 (m, 11 H)
2-88	0.65 - 0.96 (m, 26 H), 1.22 - 1.91 (m, 22 H), 2.67 - 3.06 (m, 17 H), 4.35 - 4.45 (m, 1 H), 5.09 - 5.70 (m, 11 H), 6.05 (s, 1 H), 7.11 - 7.13 (m, 2 H), 7.25 - 7.31 (m, 7 H), 7.58 - 7.60 (m, 1 H)

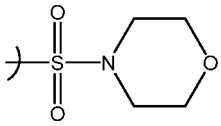
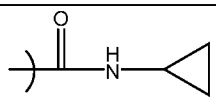
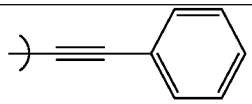
The following Formula (1C1-1) compounds (meta/para) described in Table 3 were prepared in accordance with the schemes and examples described herein.



(1C1-1)

Table 3. Formula (1C1-1) Compounds

#	3 and 3’	4 and 4’	5 and 5’
3-1	H	H	H
3-2	H	methyl	H
3-3	H	Br	H
3-4	H	phenyl	H
3-5	H	pyridin-4-yl	H
3-6	H	4-F-phenyl	H
3-7	H	4-Cl-phenyl	H
3-8	methyl	H	methyl
3-9	H	t-butyl	H
3-10	H	ethyl	H
3-11	H	-CN	H
3-12	methyl	methyl	methyl
3-13	H	$-C(O)OCH_2CH_3$	H
3-14	H	isopropyl	H
3-15	H	$-C(O)CH_3$	H
3-16	H		H
3-17	H		H
3-18	H		H
3-19	H	I	H
3-20	H		H
3-21	H	propyl	H
3-22		H	
3-23	methyl	ethyl	methyl
3-24	H		H

3-25	H		H
3-26	methyl	Cl	methyl
3-27	H	methoxy	H
3-28	methyl	propyl	methyl
3-29	H	$-CF_3$	H
3-30	isopropyl	H	isopropyl
3-31	H	$-C(O)N(CH_3)_2$	H
3-32	H	$-S(O)_2CH_3$	H
3-33	H	$-SCH(CH_3)_2$	H
3-34	methyl	$-CH_2CH_2OH$	methyl
3-35	$-CF_3$	H	$-CF_3$
3-36	-CN	H	-CN
3-37	H	F	H
3-38	H	pyridin-2-yl	H
3-39	H	-OH	H
3-40	H	$-NHC(O)CH_3$	H
3-41	H	$-NO_2$	H
3-42	H		H
3-43	H	$-CH_2CH_2OH$	H
3-44	$-CH_2OH$	H	$-CH_2OH$
3-45	methyl	$-NHC(O)CH_3$	methyl
3-46	H		H

The following Formula (1C1-1) compound and example #'s refer to those compounds depicted in Table 3. In one aspect of the invention, are Formula (1C1-1) compounds selected from the group consisting of:

(3-1). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-[[3-(pyrazol-1-ylmethyl)phenyl]methyl]-24-[[4-(pyrazol-1-

ylmethyl)phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1110);
(3-2). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-[[3-[(4-methylpyrazol-1-yl)methyl]phenyl]methyl]-24-[[4-[(4-methylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1138);
(3-3). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[(4-bromopyrazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(4-bromopyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1268);
(3-4). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-[[3-[(4-phenylpyrazol-1-yl)methyl]phenyl]methyl]-24-[[4-[(4-phenylpyrazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1262);
(3-5). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(pyridin-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(pyridin-4-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);
(3-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[[4-(4-fluorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-18-[[4-[[4-(4-fluorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1298);
(3-7). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[[4-(4-chlorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-18-[[4-[[4-(4-chlorophenyl)pyrazol-1-yl]methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1332);
(3-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);
(3-9). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[(4-tert-butylpyrazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(4-tert-butylpyrazol-1-yl)methyl]phenyl]methyl]-

3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1222);
(3-10) (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[(4-ethylpyrazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(4-ethylpyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1166);
(3-11). 1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-cyano-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-carbonitrile (1159);
(3-12). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((3,4,5-trimethyl-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((3,4,5-trimethyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(3-13). ethyl 1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-(ethoxycarbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-carboxylate (1253);
(3-14). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(3-((4-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(3-15). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-acetyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-acetyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1193);
(3-16). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(pyrrolidine-1-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(pyrrolidine-1-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1304);
(3-17). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(piperidine-1-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(piperidine-1-carbonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1332);

(3-18). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1189);
(3-19). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1361);
(3-20). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-(1H-pyrrol-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-(1H-pyrrol-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (ESI-MS m/z: 1240.4[M+H]+);
(3-21). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(3-22). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1270);
(3-23). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-ethyl-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-ethyl-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1222);
(3-24). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(piperidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(piperidin-1-ylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1404);
(3-25). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(morpholinosulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(morpholinosulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1408);
(3-26). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-

3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1234);
(3-27). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(3-((4-methoxy-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-methoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1169);
(3-28). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((3,5-dimethyl-4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3,5-dimethyl-4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);
(3-29). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1245);
(3-30). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((3,5-diisopropyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3,5-diisopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1278);
(3-31). 1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-(dimethylcarbamoyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-N,N-dimethyl-1H-pyrazole-4-carboxamide (1252);
(3-32). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(methylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(methylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1266);
(3-33). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(3-((4-(isopropylthio)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-(isopropylthio)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1258);
(3-34). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-(2-hydroxyethyl)-3,5-dimethyl-1H-pyrazol-1-

yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1254);
(3-35). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1381);
(3-36). 1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((3,5-dicyano-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-3,5-dicarbonitrile (1209);
(3-37). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1145);
(3-38). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);
(3-39). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-hydroxy-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-hydroxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1141);
(3-40). N-(1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-acetamido-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazol-4-yl)acetamide (1223);
(3-41). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1199);
(3-42). N-cyclopropyl-1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-(cyclopropylcarbamoyl)-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-

4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrazole-4-carboxamide (1276);

(3-43). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((4-(2-hydroxyethyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((4-(2-hydroxyethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197);

(3-44). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((3,5-bis(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3,5-bis(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1229);

(3-45). N-(1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((4-acetamido-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-3,5-dimethyl-1H-pyrazol-4-yl)acetamide (1280); and

(3-46). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-(3-((4-(phenylethynyl)-1H-pyrazol-1-yl)methyl)benzyl)-24-(4-((4-(phenylethynyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1310).

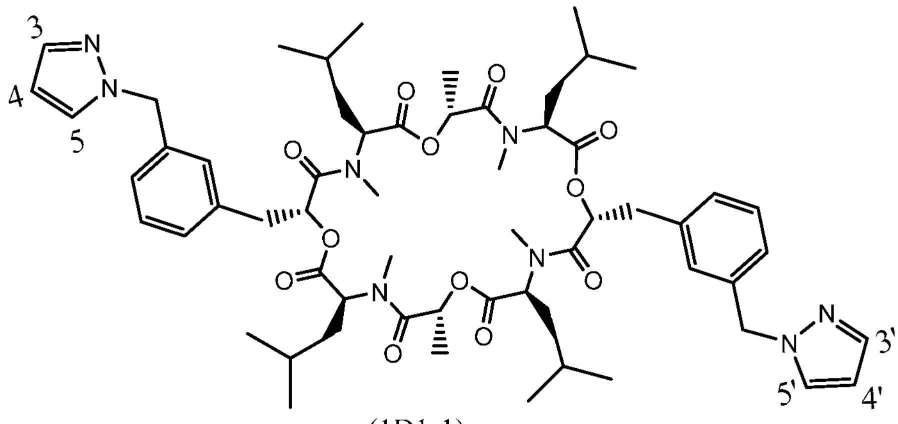
Table 3', Formula (1C1-1) Table 3 Compound NMR's (1H NMR (400Mhz, DMSO-d_6) δ ppm)

Example	NMR
3-1	0.66-0.92 (m, 26H), 1.16-1.79 (m, 16 H), 2.64-3.10 (m, 16 H), 4.39-5.73 (m, 12 H), 6.24-6.26 (m, 2 H), 7.04-7.30 (m, 8H), 7.42-7.44 (m, 2 H), 7.75-7.78 (m, 2H)
3-2	0.66-0.92 (m, 26H), 1.13-1.70 (m, 16 H), 1.96-1.98 (m ,6H) 2.67-3.08 (m, 16 H), 4.39-5.74 (m, 12 H), 6.24-6.26 (m, 2 H), 7.02-7.28 (m, 10H), 7.47-7.52 (m, 2 H)
3-3	0.65-0.96 (m, 26H), 1.15-1.76 (m, 16 H), 2.66-3.11 (m, 16 H), 4.39-5.73 (m, 12 H), 7.12-7.34 (m, 9H), 7.54-7.56 (m, 2 H), 8.02-8.04 (m, 2H)
3-4	0.62-0.94 (m, 26H), 1.12-1.78 (m, 16 H), 2.63-3.10 (m, 16 H), 4.38-5.74 (m, 12 H), 7.14-7.36 (m, 14 H), 7.54 (d, 4 H), 7.87-7.91 (m, 2 H), 8.20-8.25 (m, 2H)
3-6	0.64-0.95 (m, 26H), 1.15-1.75 (m, 16 H), 2.62-3.11 (m, 16 H), 4.38-5.75 (m, 12 H), 7.14-7.37 (m, 12 H), 7.53-7.62 (m, 4 H), 7.87-7.91 (m, 2 H), 8.20-8.24 (m, 2H)
3-7	0.64-0.94 (m, 26H), 1.15-1.73 (m, 16 H), 2.65-3.12 (m, 16 H), 4.38-5.75 (m, 12 H), 7.14-7.43 (m, 12 H), 7.56-7.61 (m, 4 H), 7.91-7.93 (m, 2 H), 8.26-8.30 (m, 2H)
3-8	0.66-0.95 (m, 26H), 1.17-1.76 (m, 16 H), 2.06-2.16 (m ,12 H) 2.67-3.09 (m, 16 H), 4.39-5.73 (m, 12 H), 5.83-5.86 (m, 2 H), 6.88-7.04 (m, 4 H), 7.14-7.28 (m, 4 H)
3-9	0.65-0.95 (m, 26H), 1.15-1.75 (m, 34 H), 2.67-3.10 (m, 16 H), 4.39-5.73 (m, 12 H), 7.07-7.34 (m, 10H), 7.54-7.57 (m, 2 H)
3-10	0.65-0.96 (m, 26H), 1.07-1.75 (m, 22 H), 2.40 (q ,4H) 2.67-3.09 (m, 16 H), 4.38-5.73 (m, 12 H), 7.05-7.32 (m, 10H), 7.50-7.55 (m, 2 H)

3-11	0.64-0.95 (m, 26H), 1.17-1.76 (m, 16 H), 2.67-3.11 (m, 16 H), 4.39-5.76 (m, 12 H), 7.14-7.36 (m, 8 H), 8.05-8.08 (m, 2 H), 8.65-8.68 (m, 2 H)
3-12	0.66-0.95 (m, 26H), 1.19-1.75 (m, 16 H), 1.84 (s, 6 H), 2.04-2.09 (m, 12 H), 2.68-3.09 (m,16H), 4.39-5.72 (m,12H), 6.89-6.94 (m,1H), 7.02 (d,2H), 7.15-7.28 (m, 5 H)
3-13	0.64-0.96 (m, 26H), 1.17-1.76 (m, 22 H), 2.67-3.11 (m, 16 H), 4.19 (q ,4H) 4.39-5.75 (m, 12 H), 7.15-7.38 (m, 8 H), 7.84-7.86 (m, 2 H), 8.39-8.42 (m, 2 H)
3-14	0.65-0.95 (m, 26H), 1.13 (d, 12 H), 1.18-1.76 (m, 16 H), 2.67-3.09 (m, 18 H), 4.39-5.72 (m, 12 H), 7.06-7.32 (m, 10 H), 7.51-7.55 (m, 2 H)
3-15	0.65-0.95 (m, 26H), 1.17-1.76 (m, 16 H), 2.33-2.36 (m, 6 H), 2.68-3.11 (m, 16 H), 4.39-5.75 (m, 12 H), 7.14-7.38 (m, 8 H), 7.91-7.93 (m, 2 H), 8.47-8.50 (m, 2 H)
3-16	0.65-0.95 (m, 26H), 1.18-1.94 (m, 24 H), 2.68-3.10 (m, 16 H), 3.40-3.43 (m, 4 H), 3.57-3.65 (m, 4 H), 4.39-5.75 (m, 12 H), 7.12-7.35 (m, 8 H), 7.77-7.80 (m, 2 H), 8.27-8.29 (m, 2 H)
3-17	0.64-0.95 (m, 26H), 1.19-1.76 (m, 28 H), 2.68-3.10 (m, 16 H), 3.52-3.54 (m, 8 H), 4.39-5.74 (m, 12 H), 7.13-7.37 (m, 8 H), 7.64 (s, 2 H), 8.12-8.15 (m, 2 H)
3-18	0.42 - 0.43 (m, 4 H), 0.66 - 0.94 (m, 28 H), 1.24 - 1.75 (m, 19 H), 2.67 - 3.04 (m, 16 H), 4.37 - 4.48 (m, 1 H), 5.01 - 5.75 (m, 12 H), 7.07 - 7.52 (m, 12 H)
3-19	0.64 - 0.93 (m, 24 H), 1.23 - 1.72 (m, 17 H), 2.68 - 3.04 (m, 16 H), 4.37 - 4.45 (m, 1 H), 5.03 - 5.76 (m, 12 H), 7.12 - 7.33 (m, 8 H), 7.52 (s, 2 H), 7.96 - 7.98 (m, 2 H)
3-21	0.79 - 0.94 (m, 28 H), 1.24 - 1.52 (m, 20 H), 2.33 - 2.36 (m, 4 H), 2.68 - 3.03 (m, 17 H), 4.41-4.48 (m, 1H), 5.10-5.74 (m,14H), 7.11 - 7.26 (m, 10 H), 7.51 - 7.53 (m, 2 H)
3-22	0.44 - 0.58 (m, 8 H), 0.67 - 0.95 (m, 32 H), 1.23 - 1.76 (m, 20 H), 2.67 - 3.03 (m, 15 H), 4.41 - 4.43 (m, 1 H), 5.09 - 5.68 (m, 14 H), 7.03 - 7.05 (m, 1 H), 7.17 - 7.19 (m, 3 H), 7.22 - 7.27 (m, 6 H)
3-23	0.73 - 1.00 (m, 26 H), 1.23 - 1.70 (m, 20 H), 2.04 - 2.07 (m, 12 H), 2.25 - 2.33 (m, 5 H), 2.68 - 3.05 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.09 - 5.68 (m, 12 H), 6.98 - 7.00 (m, 1 H), 7.13 - 7.17 (m, 2 H), 7.18 - 7.26 (m, 5 H)
3-24	0.64-0.95 (m, 26H), 1.22-1.76 (m, 28 H), 2.68-3.11 (m, 24 H), 4.39-5.75 (m, 12 H), 7.13-7.37 (m, 8 H), 7.78-7.80 (m, 2 H), 8.44-8.47 (m, 2 H)
3-25	0.65-0.95 (m, 26H), 1.18-1.76 (m, 16 H), 2.68-3.11 (m, 24 H), 3.64-3.67 (m, 8 H), 4.40-5.75 (m, 12 H), 7.14-7.38 (m, 8 H), 7.82-7.84 (m, 2 H), 8.49-8.51 (m, 2 H)
3-26	0.65 - 0.94 (m, 24 H), 1.23 - 1.68 (m, 17 H), 2.09 - 2.16 (m, 12 H), 2.67 - 3.04 (m, 16 H), 4.39 - 4.42 (m, 1 H), 5.11 - 5.68 (m, 12 H), 7.04 - 7.29 (m, 8 H)
3-27	0.69 - 0.97 (m, 24 H), 1.23 - 1.71 (m, 16 H), 2.67 - 3.03 (m, 16 H), 3.62 (s, 6 H), 4.39 - 4.42 (m, 1 H), 4.95 - 5.69 (m, 13 H), 7.07 - 7.52 (m, 12 H)
3-28	0.69 - 0.95 (m, 30 H), 1.23 - 1.69 (m, 20 H), 2.02 - 2.06 (m, 12 H), 2.22 - 2.26 (m, 4 H), 2.67 - 2.88 (m, 13 H), 2.98 - 3.09 (m, 3 H), 4.39 - 4.15 (m, 1 H), 4.95 - 5.75 (m, 13 H), 6.85 - 6.91 (m, 1 H), 6.96 - 6.98 (m, 2 H), 7.15 - 7.25 (m, 5 H)
3-29	1H NMR (400 MHz, $CDCl_3$) δ: 0.80 - 0.98 (m, 24 H), 1.38 - 1.70 (m, 16 H), 2.62 - 3.12 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.06 - 5.62 (m, 13 H), 7.17 - 7.30 (m, 8 H), 7.61 (s, 2 H), 7.71 (s, 2 H)
3-30	1H NMR (400 MHz, $CDCl_3$) δ: 0.79 - 0.96 (m, 28 H), 1.09 - 1.13 (m, 12 H), 1.24 - 1.26 (m, 12 H), 1.37 - 1.44 (m, 6 H), 1.62 - 1.71 (m, 6 H), 2.69 - 2.80 (m, 12 H), 2.93 - 3.04 (m, 8 H), 4.40 - 4.42 (m, 1 H), 5.04 - 5.59 (m, 13 H), 5.88 (s, 2 H), 6.92 - 7.16 (m, 8 H)
3-31	0.77 - 0.94 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.67 - 3.11 (m, 28 H), 4.40 - 4.42 (m, 1 H), 5.08 - 5.89 (m, 13 H), 7.20 - 7.35 (m, 8 H), 7.72 (s, 2 H), 8.20 - 8.22 (m, 2 H)
3-32	0.65 - 0.93 (m, 24 H), 1.24 - 1.71 (m, 16 H), 2.68 - 3.05 (m, 16 H), 3.18 (s, 6 H), 4.40 - 4.42 (m, 1 H), 5.10 - 581 (m, 13 H), 7.21 - 7.40 (m, 8 H), 7.92 (s, 2 H), 8.49 - 8.53 (m, 2 H)
3-33	0.65 - 0.93 (m, 24 H), 1.12 - 1.13 (m, 12 H), 1.23 - 1.66 (m, 18 H), 2.67 - 3.03 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.11 - 5.67 (m, 13 H), 7.15 - 7.28 (m, 8 H), 7.46 (s, 2 H), 7.91 - 7.94 (m, 2 H)
3-34	0.66 - 0.95 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.04 - 2.08 (m, 12 H), 2.40 - 2.44 (m, 4 H), 2.68 - 3.02 (m, 16 H), 3.31 - 3.34 (m, 4 H), 4.39 - 4.40 (m, 1 H), 5.09 - 5.68 (m, 15 H), 6.87 - 6.92 (m, 1 H), 6.99 - 7.01 (m, 2 H), 7.13 - 7.27 (m, 5 H)
3-35	0.71 - 0.92 (m, 24 H), 1.23 - 1.69 (m, 16 H), 2.67 - 3.06 (m, 16 H), 4.39 - 4.41 (m, 1 H), 5.03 - 5.71 (m, 13 H), 7.01 - 7.05 (m, 1 H), 7.11 - 7.13 (m, 2 H), 7.26 - 7.34 (m, 5 H), 7.64 (brs, 2 H)

3-36	0.65 - 0.94 (m, 24 H), 1.23 - 1.70 (m, 17 H), 2.67 - 3.07 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.81 (m, 12 H), 7.13 - 7.36 (m, 8 H), 7.99 - 8.01 (m, 2 H)
3-37	0.74 - 0.94 (m, 24 H), 1.23 - 1.75 (m, 17 H), 2.68 - 3.06 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.73 (m, 12 H), 7.11 - 7.47 (m, 10 H), 7.91 - 7.94 (m, 2 H)
3-38	0.66 - 0.92 (m, 24 H), 1.24 - 1.69 (m, 17 H), 2.65 - 3.11 (m, 16 H), 4.37 - 4.43 (m, 1 H), 5.01 - 5.75 (m, 12 H), 7.14 - 7.38 (m, 10 H), 7.62 - 7.64 (m, 2 H), 7.72 - 7.76 (m, 2 H), 8.02 - 8.03 (m, 2 H), 8.02 - 8.37 (m, 2 H), 8.47 - 8.48 (m, 2 H)
3-39	0.65 - 0.94 (m, 24 H), 1.19 - 1.70 (m, 17 H), 2.68- 3.04 (m, 16 H), 4.40 - 4.43 (m, 1 H), 5.10 - 5.70 (m, 12 H), 6.99 - 7.25 (m, 12 H), 8.39 - 8.41 (m, 2 H)
3-40	0.67 - 0.94 (m, 24 H), 1.23 - 1.81 (m, 17 H), 1.94 (s, 6 H), 2.68 - 3.03 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.07 - 5.72 (m, 12 H), 7.08 - 7.13 (m, 1 H), 7.15 - 7.19 (m, 3 H), 7.24 - 7.26 (m, 4 H), 7.37 (s, 2 H), 7.89 - 7.93 (m, 2 H), 9.92 (s, 2 H)
3-41	0.64 - 0.93 (m, 24 H), 1.23 - 1.71 (m, 17 H), 2.68 - 3.06 (m, 16 H), 4.37 - 4.48 (m, 1 H), 5.01-5.71 (m, 12 H), 7.22-7.41 (m, 8 H), 8.26-8.28 (m, 2 H), 8.99 - 9.03 (m, 2 H)
3-42	0.44 - 0.48 (m, 4 H), 0.63 - 0.94 (m, 28 H), 1.23 - 1.70 (m, 17 H), 2.68 - 3.04 (m, 18 H), 4.37-4.48 (m, 1 H), 5.02-5.70 (m, 12 H), 7.12-7.30 (m, 8 H), 8.01 - 8.17 (m, 6 H)
3-43	0.67 - 0.95 (m, 26 H), 1.24 - 1.70 (m, 17 H), 2.69 - 3.03 (m, 18 H), 3.46 - 3.50 (m, 4 H), 4.37 - 4.45 (m, 1 H), 4.57 - 4.60 (m, 2 H), 5.08 - 5.70 (m, 12 H), 7.06 - 7.28 (m, 10 H), 7.53 - 7.56 (m, 2 H)
3-44	0.68 - 1.00 (m, 24 H), 1.10 - 1.70 (m, 18 H), 2.60 - 3.20 (m, 16 H), 4.33 - 4.43 (m, 8 H), 4.9 0 - 5.80 (m, 16 H), 6.13 (s, 2 H), 6.97 - 7.23 (m, 8 H)
3-45	0.67 - 0.96 (m, 24 H), 1.23 - 1.61 (m, 18 H), 1.95 - 1.99 (m, 18 H), 2.65 - 3.15 (m, 16 H), 4.40 - 4.50 (m,1 H), 4.95 - 5.80 (m, 11 H), 6.80 - 7.10 (m, 3 H), 7.15 - 7.35 (m, 5 H), 8.95 (s, 2 H)
3-46	0.66 - 0.94 (m, 24 H), 1.23 - 1.69 (m, 16 H), 2.67 - 3.07 (m, 16 H), 4.38 - 4.40 (m, 1 H), 4.99 - 5.74 (m, 13 H), 7.14 - 7.46 (m, 18 H), 7.71 (brs, 2 H), 8.15 - 8.18 (m, 2 H)

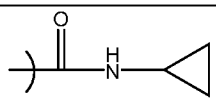
The following Formula (1D1-1) compounds (meta/meta; bis) described in Table 4 were prepared in accordance with the schemes and examples described herein.



(1D1-1)

Table 4. Formula (1D1-1) Symmetrical Compounds

#	3 and 3’	4 and 4’	5 and 5’
4-1	H	H	H
4-2	H	Br	H
4-3	H	I	H

4-4	H	propyl	H
4-5		H	
4-6	methyl	ethyl	methyl
4-7	H	$-CF_3$	H
4-8	methyl	Cl	methyl
4-9	H	$-OCH_3$	H
4-10	methyl	propyl	methyl
4-11	H	$-S(O)_2CH_3$	H
4-12	H	$-SCH(CH_3)_2$	H
4-13	$-CF_3$	H	$-CF_3$
4-14	CN	H	CN
4-15	H	$-NO_2$	H
4-16	H	pyridin-2-yl	H
4-17	H	-OH	H
4-18	H		H
4-19	H	$-CH_2CH_2OH$	H
4-20	methyl	$-NHC(O)CH_3$	methyl

The following Formula (1D1-1) compound names and example #'s refer to those compounds depicted in Table 4. In one aspect of the invention, are Formula (1D1-1) compounds selected from the group consisting of:

(4-1). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1109);

(4-2). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((4-bromo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1267);

(4-3). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1361);

(4-4). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(3-((4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(4-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1270);
(4-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((4-ethyl-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1222);
(4-7). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(3-((4-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1245);
(4-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1234);
(4-9). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(3-((4-methoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1169);
(4-10). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((3,5-dimethyl-4-propyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);
(4-11). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(3-((4-(methylsulfonyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1266);
(4-12). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(3-((4-(isopropylthio)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1258);

(4-13). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1381);

(4-14). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(3,1-phenylene))bis(methylene))bis(1H-pyrazole-3,5-dicarbonitrile) (1209);

(4-15). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(3-((4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1199);

(4-16). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(3-((4-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);

(4-17). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((4-hydroxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1141);

(4-18). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(3,1-phenylene))bis(methylene))bis(N-cyclopropyl-1H-pyrazole-4-carboxamide) (1276);

(4-19). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(3-((4-(2-hydroxyethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197); and

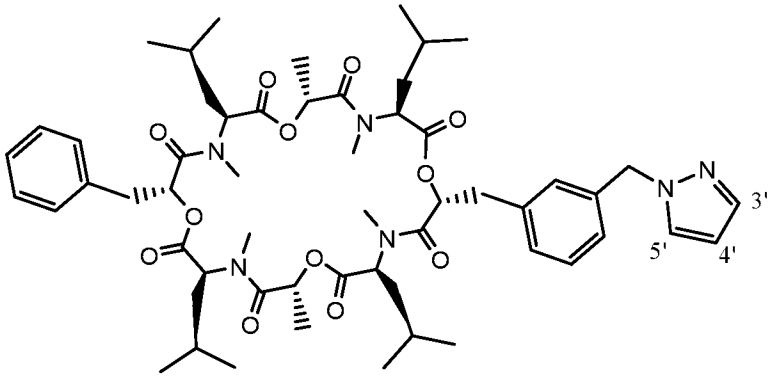
(4-20). N,N'-((((((2R,5S,8S,11S,14R,17S,20S,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(3,1-phenylene))bis(methylene))bis(3,5-dimethyl-1H-pyrazole-1,4-diyl))diacetamide (1280).

Table 4'. Formula (1D1-1) Table 4 Compound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

Example	NMR
4-1	0.67 - 0.97 (m, 24 H), 1.23 - 1.75 (m, 17 H), 2.68 - 3.26 (m, 16 H), 4.37 - 4.48 (m, 1 H), 5.01 - 5.75 (m, 12 H), 6.24 - 6.25 (m, 2 H), 7.05 - 7.44 (m, 10 H), 7.71 - 7.76 (m, 2 H)
4-2	0.65 - 0.94 (m, 24 H), 1.23 - 1.75 (m, 17 H), 2.67 - 3.04 (m, 16 H), 4.37 - 4.45 (m, 1 H), 5.01 - 5.75 (m, 12 H), 7.05 - 7.30 (m, 8 H), 7.53 - 7.54 (m, 2 H), 7.90 - 8.05 (m, 2 H)
4-3	0.65 - 0.97 (m, 24 H), 1.23 - 1.75 (m, 17 H), 2.68 - 3.04 (m, 16 H), 4.37 - 4.45 (m, 1 H), 5.01 - 5.70 (m, 12 H), 7.17 - 7.29 (m, 8 H), 7.51 - 7.53 (m, 2 H), 7.92 - 7.96 (m, 2 H)
4-4	0.87 - 0.97 (m, 28 H), 1.23 - 1.69 (m, 20 H), 2.31 - 2.38 (m, 5 H), 2.68 - 3.26 (m, 16 H), 4.41 - 4.48 (m, 1 H), 5.11 - 5.60 (m, 14 H), 7.11 - 7.13 (m, 4 H), 7.23 - 7.29 (m, 6 H), 7.45 - 7.51 (m, 2 H)
4-5	0.44 - 0.54 (m, 8 H), 0.70 - 0.98 (m, 32 H), 1.21 - 1.75 (m, 20 H), 2.67 - 3.05 (m, 15 H), 4.41 - 4.43 (m, 1 H), 5.05 - 5.59 (m, 14 H), 6.73 - 6.87 (m, 2 H), 7.03 - 7.05 (m, 2 H), 7.21 - 7.27 (m, 6 H)
4-6	0.72 - 1.00 (m, 26 H), 1.24 - 1.69 (m, 20 H), 2.04 - 2.10 (m, 12 H), 2.27 - 2.32 (m, 5 H), 2.68 - 3.08 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.12 - 5.36 (m, 12 H), 6.98 - 7.00 (m, 1 H), 7.18 - 7.20 (m, 2 H), 7.22 - 7.26 (m, 5 H)
4-7	1H NMR (400 MHz, $CDCl_3$) δ: 0.80 - 0.93 (m, 20 H), 0.98 - 1.76 (m, 20 H), 2.63 - 3.11 (m, 18 H), 4.41 - 4.43 (m, 1 H), 5.28 - 5.61 (m, 11 H), 7.20 - 7.71 (m, 12 H)
4-8	0.67 - 0.97 (m, 24 H), 1.23 - 1.71 (m, 17 H), 2.03 - 2.18 (m, 12 H), 2.67 - 3.04 (m, 16 H), 4.39 - 4.42 (m, 1 H), 5.11 - 5.44 (m, 12 H), 7.04 - 7.28 (m, 8 H)
4-9	0.69 - 0.97 (m, 24 H), 1.23 - 1.70 (m, 16 H), 2.67 - 3.32 (m, 16 H), 3.62 (s, 6 H), 4.39 - 4.51 (m, 1 H), 4.95 - 5.69 (m, 13 H), 6.98 - 7.49 (m, 12 H)
4-10	0.74 - 0.97 (m, 30 H), 1.23 - 1.69 (m, 20 H), 2.02 - 2.08 (m, 12 H), 2.22 - 2.26 (m, 4 H), 2.67 - 3.25 (m, 16 H), 4.41 - 4.48 (m, 1 H), 5.09 - 5.64 (m, 13 H), 6.71 - 6.79 (m, 1 H), 6.69 - 6.98 (m, 2 H), 7.18 - 7.25 (m, 5 H)
4-11	0.71 - 0.97 (m, 24 H), 1.23 - 1.74 (m, 16 H), 2.67 - 3.06 (m, 16 H), 3.18 - 3.19 (m, 6 H), 4.40 - 4.43 (m, 1 H), 5.10 - 5.52 (m, 13 H), 7.25 - 7.34 (m, 8 H), 7.91 - 7.93 (m, 2 H), 8.45 - 8.51 (m, 2 H)
4-12	0.74 - 0.94 (m, 24 H), 1.12 - 1.13 (m, 12 H), 1.23 - 1.66 (m, 18 H), 2.67 - 3.03 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.11 - 5.67 (m, 13 H), 7.08 - 7.29 (m, 8 H), 7.46 (s, 2 H), 7.85 - 7.9 (m, 2 H)
4-13	0.76 - 0.96 (m, 24 H), 1.23 - 1.72 (m, 16 H), 2.66 - 3.05 (m, 16 H), 4.39 - 4.42 (m, 1 H), 5.04 - 5.71 (m, 13 H), 6.72 - 6.82 (m, 1 H), 7.11 - 7.13 (m, 2 H), 7.25 - 7.37 (m, 5 H), 7.63 - 7.69 (m, 2 H)
4-14	0.68 - 0.97 (m, 24 H), 1.23 - 1.73 (m, 17 H), 2.66 - 3.25 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.01 - 5.81 (m, 12 H), 7.03 - 7.42 (m, 8 H), 7.98 - 8.02 (m, 2 H)
4-15	0.67 - 0.96 (m, 24 H), 1.23 - 1.57 (m, 17 H), 2.68 - 2.91 (m, 16 H), 4.47 - 4.53 (m, 1 H), 5.08 - 5.73 (m, 12 H), 7.23 - 7.33 (m, 8 H), 8.26-8.28 (m, 2 H), 8.96 - 9.01 (m, 2 H)
4-16	0.69 - 0.95 (m, 24 H), 1.25 - 1.81 (m, 17 H), 2.66 - 3.20 (m, 16 H), 4.41 - 4.42 (m, 1 H), 5.03 - 5.70 (m, 12 H), 7.15 - 8.47 (m, 20 H)
4-17	0.67 - 0.97 (m, 24 H), 1.24 - 1.75 (m, 17 H), 2.68 - 3.04 (m, 16 H), 4.37 - 4.48 (m, 1 H), 5.01 - 5.75 (m, 12 H), 6.98 - 7.27 (m, 12 H), 8.39 - 8.44 (m, 2 H)
4-18	0.40 - 0.48 (m, 4 H), 0.60 - 1.00 (m, 28 H), 1.15 - 1.80 (m, 20 H), 2.65 - 3.15 (m, 16 H), 4.35 - 4.42 (m, 1 H), 5.00 - 5.80 (m, 11 H), 7.15 - 7.40 (m, 8 H), 7.80 (s, 2 H), 8.00 - 8.30 (m, 4 H)
4-19	0.65 - 1.00 (m, 24 H), 1.15 - 1.80 (m, 18 H), 2.70 - 3.10 (m, 16 H), 3.45 - 3.55 (m, 4 H), 4.40 - 4.50 (m, 2 H), 4.55 - 4.65 (m, 2 H), 5.05 - 5.80 (m, 14 H), 7.05 - 7.10 (m, 4 H), 7.20 - 7.40 (m, 6 H), 7.50 - 7.60 (m, 2 H)

4-20	0.68 - 0.98 (m, 24 H), 1.23 - 1.68 (m, 18 H), 1.95 - 2.01(m, 18 H), 2.67 - 2.98 (m, 16 H), 4.40 - 4.50 (m, 1 H), 5.00 - 5.80 (m, 11 H), 6.68 - 6.78 (m, 1 H), 6.98 - 7.05 (m, 2 H), 7.15 - 7.40 (m, 5 H), 8.02 - 8.80 (m, 2 H)

The following Formula (1E1) compounds (meta hybrids) described in Table 5 were prepared in accordance with the schemes and examples described herein.



(1E1)

Table 5. Formula (1E1) Compounds

#	3'	4'	5'
5-1	H	F	H
5-2	H	$-NO_2$	H
5-3	H	-OH	H
5-4	$-CH_2OH$	H	$-CH_2OH$
5-5	methyl	$-NHC(O)CH_3$	methyl
5-6		H	

The following Formula (1E1) compound names and example #'s refer to those compounds depicted in Table 5. In one aspect of the invention, are Formula (1E1) compounds selected from the group consisting of:

(5-1). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(3-((4-fluoro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1047);

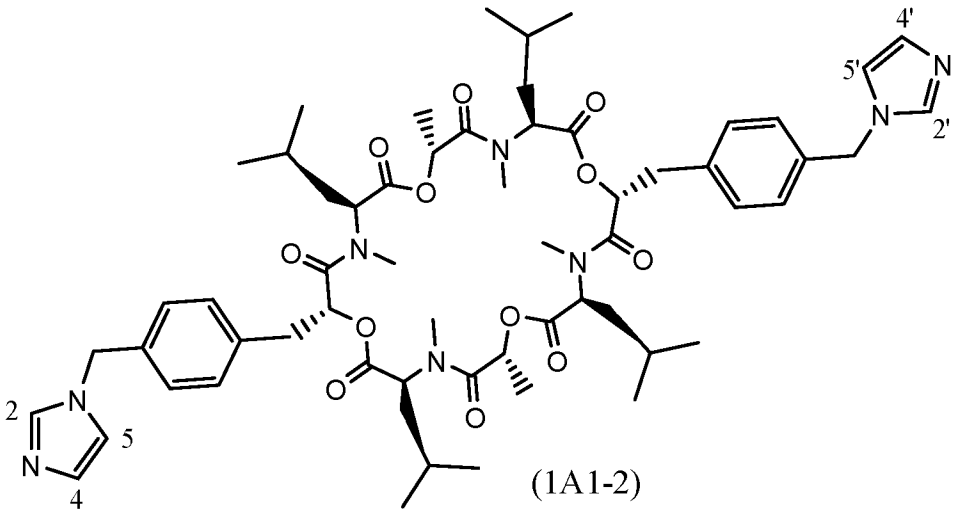
(5-2). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(3-((4-nitro-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1074);

(5-3). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(3-((4-hydroxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1045);
(5-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(3-((3,5-bis(hydroxymethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1089);
(5-5). N-(1-(3-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-3,5-dimethyl-1H-pyrazol-4-yl)acetamide (1114); and
(5-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(3-((3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1109).

Table 5'. Formula (1E1) Table 5 Coumpound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

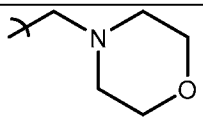
Example	NMR
5-1	0.67 - 0.96 (m, 24 H), 1.23 - 1.62 (m, 17 H), 2.69 - 3.09 (m, 16 H), 4.41 - 4.43 (m, 1 H), 5.06 - 5.70 (m, 10 H), 7.11 - 7.13 (m, 1 H), 7.25 - 7.31 (m, 8 H), 7.47 - 7.48 (m, 1 H), 7.93 - 7.94 (m, 1 H)
5-2	0.64 - 0.96 (m, 24 H), 1.21 - 1.70 (m, 17 H), 2.67 - 3.07 (m, 16 H), 4.37 - 4.48 (m, 1 H), 5.01 - 5.75 (m, 10 H), 7.22 - 7.42 (m, 9 H), 8.26 - 8.27 (m, 1 H), 9.02 - 9.03 (m, 1 H)
5-3	0.65 - 0.96 (m, 24 H), 1.23 - 1.71 (m, 17 H), 2.67 - 3.08 (m, 16 H), 4.38 - 4.48 (m, 1 H), 5.01 - 5.75 (m, 10 H), 6.99 - 7.31 (m, 11 H), 8.39 - 8.41 (m, 1 H)
5-4	0.65 - 1.00 (m, 24 H), 1.05 - 1.75 (m, 18 H), 2.65 - 3.10 (m, 16 H), 4.33 - 4.42 (m, 4 H), 4.90-5.80 (m,12 H), 6.15 (s,1H), 6.98-7.05 (m, 2 H), 7.15-7.40 (m, 7 H)
5-5	0.65 - 0.96 (m, 24 H), 1.15 - 1.70 (m, 17 H), 1.96 - 2.00 (m, 9 H), 2.69 - 3.06 (m, 16 H), 4.40 - 4.45 (m, 1 H), 5.03 - 5.70 (m, 10 H), 6.92 - 7.05 (m, 2 H), 7.18 - 7.31 (m, 7 H), 8.95 (brs, 1 H)
5-6	0.46 - 0.54 (m, 4 H), 0.70 - 0.96 (m, 28 H), 1.24 - 1.74 (m, 19 H), 2.68 - 3.06 (m, 16 H), 4.40 - 4.43 (m, 1 H), 5.03 - 5.70 (m, 10 H), 6.92 - 7.31 (m, 10 H)

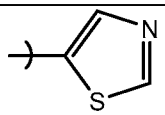
The following Formula (1A1-2) compounds (para/para; bis) described in Table 6 were prepared in accordance with the schemes and examples described herein.



(1A1-2)

Table 6. Formula (1A1-2) Symmetrical Compounds

Ex	2 and 2'	4 and 4'	5 and 5'
6-1	methyl	H	H
6-2	H	H	H
6-3	Br	H	H
6-4	ethyl	H	H
6-5	methyl	methyl	H
6-6	t-butyl	H	H
6-7		H	H
6-8	isopropyl	H	H
6-9	Cl	H	H
6-10	I	H	H
6-11	phenyl	H	H
6-12	H	Br	H
6-13	H	methyl	methyl
6-14	H	methyl	H
6-15	$-CF_3$	H	H
6-16	$-CH_2OH$	H	H
6-17		H	H

6-18		H	H
6-19	$-CH_2OCH_3$	H	H
6-20	$-CH_2OCH_2CH_3$	H	H

The following Formula (1A1-2) compound names and example #'s refer to those compounds depicted in Table 6. In one aspect of the invention, are Formula (1A1-2) compounds selected from the group consisting of:

(6-1). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-[(2-methylimidazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1138); .

(6-2). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-(imidazol-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1110);

(6-3). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(2-bromoimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1268);

(6-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(2-ethylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1166);

(6-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2,4-dimethyl-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);

(6-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(2-tert-butylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1222);

(6-7). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(2-cyclopropylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1190);
(6-8). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((2-isopropyl-1H-imidazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);
(6-9). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2-chloro-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1178);
(6-10). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2-iodo-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1361);
(6-11). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((2-phenyl-1H-imidazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1262);
(6-12). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-bromo-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1267);
(6-13). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4,5-dimethyl-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);
(6-14). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-methyl-1H-imidazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1137);
(6-15). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((2-(trifluoromethyl)-1H-imidazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1245);
(6-16). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2-(hydroxymethyl)-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1169);
(6-17). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((2-(morpholinomethyl)-1H-imidazol-1-yl)methyl)benzyl)-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1308);

(6-18). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((2-(thiazol-5-yl)-1H-imidazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1276);

(6-19). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((2-(methoxymethyl)-1H-imidazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1197); and

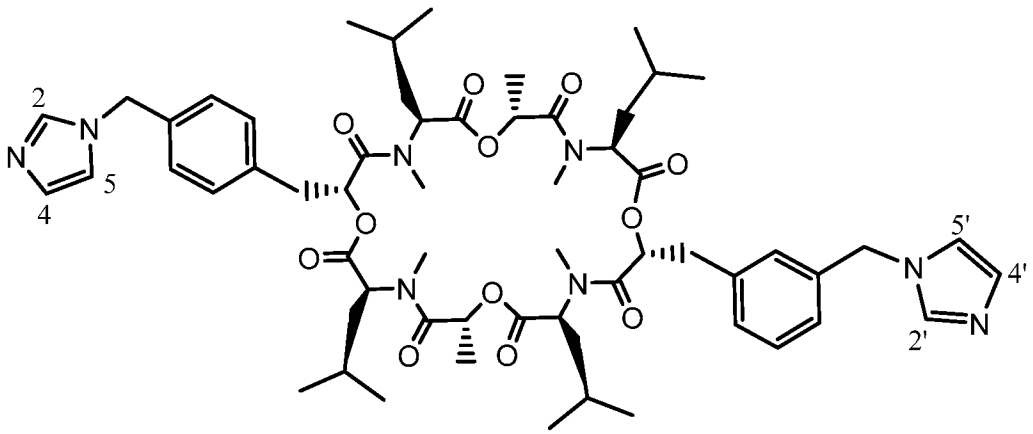
(6-20). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2-(ethoxymethyl)-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1226).

Table 6'. Formula (1A1-2) Table 6 Compound NMRs (1H NMR (400MHz, DMSO-d_6) δ ppm)

Example	NMR
6-1	0.69-0.96 (m, 26H), 1.20-1.76 (m, 16 H), 2.57 (s, 6H), 2.65-3.12 (m, 16 H), 4.38-5.74 (m,12H), 7.28-7.31 (m,4H), 7.34-7.39 (m, 4 H), 7.60 (d, 2 H), 7.64-7.67 (m, 2H)
6-2	0.65-0.98 (m, 26H), 1.15-1.74 (m, 16 H), 2.66-3.11 (m, 16 H), 4.38-5.75 (m, 12 H), 7.34-7.42 (m, 8 H), 7.72 (d, 4 H), 9.25 (s, 2H)
6-3	0.68-0.95 (m, 26H), 1.20-1.74 (m, 16 H), 2.67-3.09 (m, 16 H), 4.38-5.73 (m, 12 H), 7.03-7.05 (m, 2 H), 7.14 (d, 4 H), 7.32 (dd, 4 H), 7.45-7.47 (m, 2H)
6-4	0.68-0.95 (m, 26H), 1.14-1.75 (m, 22 H), 2.67-3.11 (m, 20 H), 4.38-5.73 (m, 12 H), 7.26-7.31 (m, 4 H), 7.37 (d, 4 H), 7.64-7.71 (m, 4H)
6-5	0.69-0.94 (m, 26H), 1.21-1.76 (m, 16 H), 2.20 (s, 6 H), 2.54 (s, 6 H), 2.67-3.11 (m, 16 H), 4.39-5.73 (m, 12 H), 7.27-7.39 (m, 10 H)
6-6	0.69-0.95 (m, 26H), 1.24-1.77 (m, 34 H), 2.66-3.10 (m, 16 H), 4.39-5.69 (m, 12 H), 7.09-7.14 (m, 4 H), 7.37 (d, 4 H), 7.54-7.56 (m, 2H), 7.66-7.68 (m, 2 H)
6-7	0.69-0.94 (m, 26H), 1.04-1.75 (m, 24 H), 2.31-2.38 (m, 2 H), 2.67-3.11 (m, 16 H), 4.39-5.74 (m, 12 H), 7.30-7.38 (m, 8 H), 7.57 (d, 2 H), 7.69 (d, 2H)
6-8	0.70-0.94 (m, 26H), 1.16-1.77 (m, 28 H), 2.66-3.11 (m, 16 H), 3.46-3.54 (m, 2 H), 4.39-5.71 (m, 12 H), 7.26-7.38 (m, 8 H), 7.69-7.73 (m, 4 H)
6-9	0.69-0.95 (m, 26H), 1.19-1.74 (m, 16 H), 2.67-3.09 (m, 16 H), 4.39-5.72 (m, 12 H), 6.92-6.94 (m, 2 H), 7.15 (d, 4 H), 7.30-7.39 (m, 6 H)
6-10	0.69-0.96 (m, 26H), 1.20-1.75 (m, 16 H), 2.67-3.11 (m, 16 H), 4.39-5.73 (m, 12 H), 7.17-7.21 (m, 4 H), 7.32-7.37 (m, 4 H), 7.46-7.50 (m, 2 H), 7.71-7.75 (m, 2 H)
6-11	0.64-0.92 (m, 26H), 1.19-1.75 (m, 16 H), 2.67-3.07 (m, 16 H), 4.38-5.69 (m, 12 H), 7.06 (d, 4 H), 7.27-7.31 (m, 4 H), 7.60-7.73 (m, 10 H), 7.83-7.89 (m, 4 H)
6-12	0.69-0.96 (m, 26H), 1.20-1.76 (m, 16 H), 2.67-3.10 (m, 16 H), 4.39-5.72 (m, 12 H), 7.18-7.21 (m, 4 H), 7.32-7.37 (m, 4 H), 7.48-7.62 (m, 2 H), 8.67-8.79 (m, 2 H)
6-13	0.69-0.96 (m, 26H), 1.19-1.75 (m, 16 H), 2.06 (s, 6 H), 2.19 (s, 6 H), 2.67-3.11 (m, 16 H), 4.39-5.73 (m, 12 H), 7.22-7.26 (m, 4 H), 7.34-7.39 (m, 4 H), 9.09 (s, 2 H)
6-14	0.67-0.95 (m, 26H), 1.20-1.75 (m, 16 H), 2.23 (s, 6 H), 2.67-3.11 (m, 16 H), 4.39-5.75 (m, 12 H), 7.24-7.47 (m, 10 H), 9.11-9.13 (m, 2 H)

6-15	0.69-0.94 (m, 26H), 1.20-1.76 (m, 16 H), 2.66-3.09 (m, 16 H), 4.38-5.71 (m, 12 H), 7.09-7.15 (m, 6 H), 7.29-7.34 (m, 4 H), 7.57-7.59 (m, 2H)
6-16	0.69-0.94 (m, 26H), 1.20-1.75 (m, 16 H), 2.67-3.11 (m, 16 H), 4.39-5.74 (m, 16 H), 7.31-7.38 (m, 8 H), 7.63-7.67 (m, 4 H)
6-19	0.69-0.95 (m, 26H), 1.20-1.76 (m, 16 H), 2.67-3.12 (m, 16 H), 3.33 (s, 6 H), 4.40-5.74 (m, 16 H), 7.31-7.38 (m, 8 H), 7.68-7.74 (m, 4 H)
6-20	0.69-0.94 (m, 26H), 1.09-1.14 (m, 6 H), 1.20-1.76 (m, 16 H), 2.67-3.12 (m, 16 H), 3.50-3.56 (m, 4 H), 4.39-5.74 (m, 16 H), 7.32-7.38 (m, 8 H), 7.68-7.74 (m, 4 H)

The following Formula (1C1-2) compounds (meta/para) described in Table 7 were prepared in accordance with the schemes and examples described herein.



(1C1-2)

Table 7. Formula (1C1-2) Compounds

#	2 and 2'	4 and 4'	5 and 5'
7-1	methyl	H	H
7-2	H	H	H
7-3	Br	H	H
7-4	ethyl	H	H
7-5	methyl	methyl	H
7-6	t-butyl	H	H
7-7		H	H
7-8	isopropyl	H	H
7-9	Cl	H	H
7-10	I	H	H
7-11	$-CH_2OH$	H	H

The following Formula (1C1-2) compound names and example #'s refer to those compounds depicted in Table 7. In one aspect of the invention, are Formula (1C1-2) compounds selected from the group consisting of:

(7-1). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12-[[3-[(2-methylimidazol-1-yl)methyl]phenyl]methyl]-24-[[4-[(2-methylimidazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1138);

(7-2). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((1H-imidazol-1-yl)methyl)benzyl)-18-(4-((1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1109);

(7-3). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[(2-bromoimidazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(2-bromoimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1268);

(7-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[(2-ethylimidazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(2-ethylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1166);

(7-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((2,4-dimethyl-1H-imidazol-1-yl)methyl)benzyl)-18-(4-((2,4-dimethyl-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1165);

(7-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((2-(tert-butyl)-1H-imidazol-1-yl)methyl)benzyl)-18-(4-((2-(tert-butyl)-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1222);

(7-7). (3S,6R,9S,12R,15S,18R,21S,24R)-6-[[3-[(2-cyclopropylimidazol-1-yl)methyl]phenyl]methyl]-18-[[4-[(2-cyclopropylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1190);

(7-8). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6-(3-((2-isopropyl-1H-imidazol-1-yl)methyl)benzyl)-18-(4-((2-isopropyl-1H-imidazol-1-yl)methyl)benzyl)-

4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1194);

(7-9). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((2-chloro-1H-imidazol-1-yl)methyl)benzyl)-18-(4-((2-chloro-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1178);

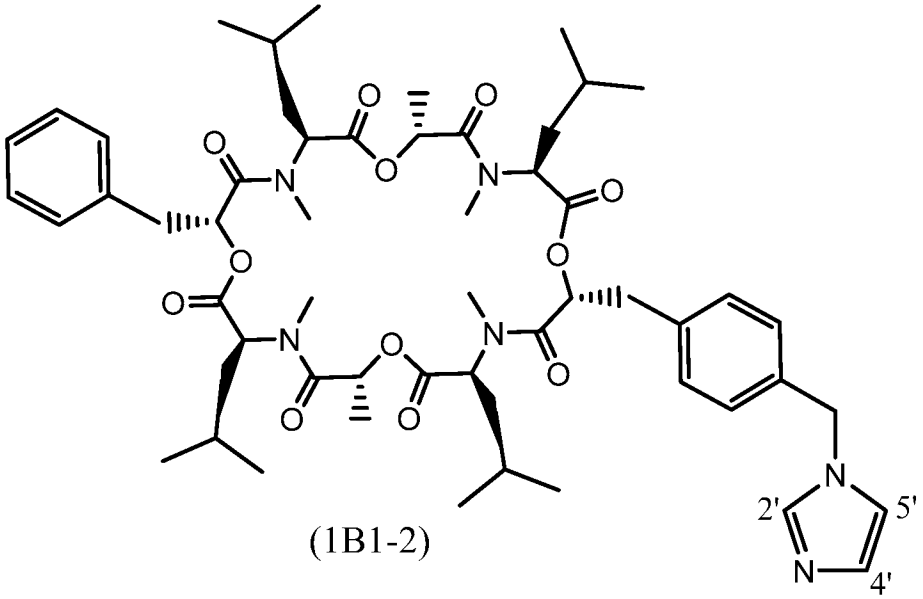
(7-10). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((2-iodo-1H-imidazol-1-yl)methyl)benzyl)-18-(4-((2-iodo-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1361); and

(7-11). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(3-((2-(hydroxymethyl)-1H-imidazol-1-yl)methyl)benzyl)-18-(4-((2-(hydroxymethyl)-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1169).

Table 7'. Formula (1C1-2) Table 7 Compound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

Example	NMR
7-1	0.64-0.96 (m, 26H), 1.21-1.76 (m, 16 H), 2.56-2.62 (m, 6H) 2.64-3.10 (m, 16 H), 4.39-5.77 (m, 12 H), 7.23-7.44 (m, 8H), 7.57-7.67 (m, 4 H)
7-2	0.63-0.94 (m, 26H), 1.19-1.76 (m, 16 H), 2.68-3.16 (m, 16 H), 4.39-5.77 (m, 12 H), 7.30-7.52 (m, 8 H), 7.68-7.78 (m, 4 H), 9.25 (s, 2 H)
7-3	0.64-0.95 (m, 26 H), 1.17-1.77 (m, 16 H), 2.67-3.10 (m, 16 H), 4.39-5.75 (m, 12 H), 7.04-7.35 (m, 10 H), 7.46-7.49 (m, 2 H)
7-4	0.65-0.95 (m, 26 H), 1.14-1.77 (m, 22 H), 2.67-3.14 (m, 20 H), 4.39-5.76 (m, 12 H), 7.20-7.43 (m, 8 H), 7.63-7.71 (m, 4 H)
7-5	0.65-0.94 (m, 26 H), 1.22-1.77 (m, 16 H), 2.20 (s, 6 H), 2.58 (s, 6 H), 2.68-3.12 (m, 16 H), 4.39-5.79 (m, 12 H), 7.21-7.43 (m, 10 H)
7-6	0.70-0.95 (m, 26 H), 1.23-1.78 (m, 34 H), 2.67-3.11 (m, 16 H), 4.39-5.73 (m, 12 H), 7.10-7.13 (m, 2H), 7.28-7.39 (m, 6H), 7.49-7.56 (m, 2 H), 7.66-7.70 (m, 2 H)
7-7	0.66-0.94 (m, 26 H), 1.04-1.76 (m, 24 H), 2.31-2.38 (m, 2 H), 2.68-3.14 (m, 16 H), 4.39-5.78 (m, 12H), 7.22-7.47 (m,8H), 7.55-7.57 (m,2 H), 7.69-7.71 (m, 2 H)
7-8	0.67-0.94 (m, 26 H), 1.16-1.78 (m, 28 H), 2.67-3.12 (m, 16 H), 3.46-3.56 (m, 2 H), 4.39-5.75 (m, 12 H), 7.16-7.45 (m, 8 H), 7.68-7.73 (m, 4 H)
7-9	0.66-0.94 (m, 26 H), 1.20-1.75 (m, 16 H), 2.68-3.11 (m, 16 H), 4.39-5.75 (m, 12 H), 6.93-6.95 (m, 2 H), 7.05-7.34 (m, 8 H), 7.39-7.41 (m, 2 H)
7-10	0.67-0.95 (m, 26 H), 1.18-1.76 (m, 16 H), 2.68-3.13 (m, 16 H), 4.39-5.75 (m, 12 H), 7.09-7.50 (m, 10 H), 7.68-7.73 (m, 2 H)
7-11	0.65-0.95 (m, 26 H), 1.18-1.76 (m, 16 H), 2.68-3.13 (m, 16 H), 4.39-5.76 (m, 16 H), 7.25-7.47 (m, 8 H), 7.62-7.70 (m, 4 H)

The following Formula (1B1-2) compounds (hybrid analogs) described in Table 8 were prepared in accordance with the schemes and examples described



(1B1-2)

herein.

Table 8. Formula (1B1-2) Compounds

#	2'	4'	5'
8-1	methyl	H	H
8-2	H	H	H
8-3	Br	H	H
8-4	ethyl	H	H
8-5	methyl	methyl	H
8-6	t-butyl	H	H
8-7		H	H
8-8	isopropyl	H	H
8-9	Cl	H	H
8-10	I	H	H
8-11	H	methyl	methyl
8-12	$-CF_3$	H	H
8-13	$-CH_2OH$	H	H
8-14	$-CH_2F$	H	H
8-15	H	Br	H

The following Formula (1B1-2) compound names and example #'s refer to those compounds depicted in Table 8. In one aspect of the invention, are Formula (1B1-2) compounds selected from the group consisting of:

(8-1). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-[[4-[(2-methylimidazol-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1043);

(8-2). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-(imidazol-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1029);

(8-3). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[(2-bromoimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1108);

(8-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[(2-ethylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1058);

(8-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((2,4-dimethyl-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1057);

(8-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[(2-tert-butylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1086);

(8-7). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-[(2-cyclopropylimidazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1069);

(8-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-18-(4-((2-isopropyl-1H-imidazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1071);

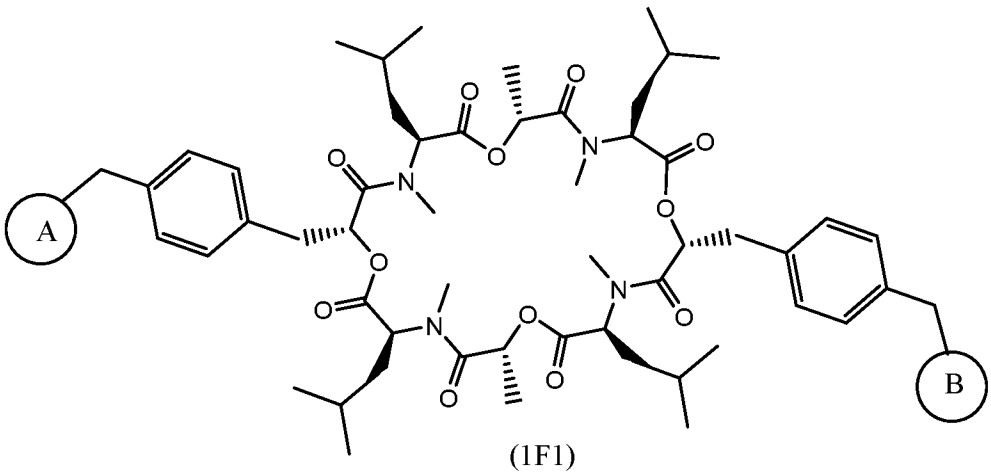
(8-9). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((2-chloro-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1064);
(8-10). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((2-iodo-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1155);
(8-11). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4,5-dimethyl-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1057);
(8-12). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((2-(trifluoromethyl)-1H-imidazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1097);
(8-13). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((2-(hydroxymethyl)-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1059);
(8-14). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((2-(fluoromethyl)-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1061); and
(8-15). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-bromo-1H-imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1108).

Table 8'. Formula (1B1-2) Table 8 Compound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

Example	NMR
8-1	0.69-0.96 (m, 26H), 1.20-1.76 (m, 16 H), 2.57 (s, 3H), 2.65-3.11 (m, 16 H), 4.38-5.76 (m, 10 H), 7.22-7.38 (m, 9H), 7.59-7.66 (m, 2H)
8-2	0.65-0.96 (m, 26H), 1.17-1.77 (m, 16 H), 2.66-3.12 (m, 16 H), 4.38-5.75 (m, 10 H), 7.22-7.41 (m, 9H), 7.72 (d, 2H), 9.25 (s, 1H)
8-3	0.69-0.98 (m, 26H), 1.20-1.77 (m, 16 H), 2.66-3.12 (m, 16 H), 4.39-5.75 (m, 10 H), 7.02 (s, 1 H), 7.14 (d, 2 H), 7.23-7.35 (m, 7H), 7.45-7.47 (m, 1H)

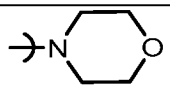
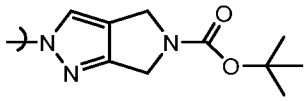
8-4	0.66-0.96 (m, 26H), 1.14-1.76 (m, 19 H), 2.67-3.11 (m, 18 H), 4.39-5.75 (m, 10 H), 7.22-7.39 (m, 9H), 7.65-7.71 (m, 2H)
8-5	0.69-0.96 (m, 26 H), 1.20-1.76 (m, 16 H), 2.20 (s, 3 H), 2.54 (s, 3 H), 2.68-3.11 (m, 16 H), 4.38-5.75 (m, 10 H), 7.22-7.39 (m, 10 H)
8-6	0.67-0.96 (m, 26 H), 1.21-1.77 (m, 25 H), 2.66-3.11 (m, 16 H), 4.39-5.75 (m, 10 H), 7.10-7.39 (m, 9 H), 7.54-7.56 (m, 1 H), 7.67-7.68 (m, 1 H)
8-7	0.68-0.96 (m, 26H), 1.04-1.77 (m, 20 H), 2.31-2.38 (m, 1 H), 2.67-3.11 (m, 16 H), 4.39-5.75 (m, 10 H), 7.22-7.38 (m, 9H), 7.57 (d, 1 H), 7.69 (d, 1 H)
8-8	0.69-0.96 (m, 26 H), 1.16-1.77 (m, 22 H), 2.66-3.11 (m, 16 H), 3.47-3.55 (m, 1 H), 4.39-5.75 (m, 10 H), 7.22-7.39 (m, 9H), 7.70-7.73 (m, 2 H)
8-9	0.69-0.96 (m, 26 H), 1.20-1.76 (m, 16 H), 2.67-3.11 (m, 16 H), 4.39-5.75 (m, 10 H), 6.92 (s, 1 H), 7.14-7.39 (m, 10 H)
8-10	0.69-0.96 (m, 26 H), 1.20-1.76 (m, 16 H), 2.67-3.11 (m, 16 H), 4.39-5.75 (m, 10 H), 7.15-7.49 (m, 10 H), 7.71-7.75 (m, 1 H)
8-11	0.69-0.96 (m, 26 H), 1.20-1.76 (m, 16 H), 2.06 (s, 3 H), 2.18 (s, 3 H), 2.66-3.12 (m, 16 H), 4.38-5.75 (m, 10 H), 7.22-7.38 (m, 9 H), 9.09 (s, 1 H)
8-12	0.69-0.96 (m, 26 H), 1.20-1.76 (m, 16 H), 2.67-3.10 (m, 16 H), 4.39-5.75 (m, 10 H), 7.10-7.16 (m, 3 H), 7.23-7.35 (m, 7 H), 7.58-7.60 (m, 1 H)
8-13	0.69-0.96 (m, 26 H), 1.19-1.76 (m, 16 H), 2.68-3.12 (m, 16 H), 4.40-5.75 (m, 12 H), 7.22-7.38 (m, 9 H), 7.64-7.67 (m, 2 H)
8-14	0.69-0.96 (m, 26 H), 1.19-1.75 (m, 16 H), 2.67-3.11 (m, 16 H), 4.38-5.79 (m, 12 H), 7.23-7.38 (m, 9 H), 7.62 (s, 1 H), 7.72 (s, 1 H)
8-15	0.68-0.96 (m, 26 H), 1.19-1.79 (m, 16 H), 2.67-3.13 (m, 16 H), 4.39-5.75 (m, 10 H), 7.17-7.36 (m, 9 H), 7.43-7.55 (m, 1 H), 8.55-8.73 (m, 1 H)

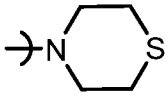
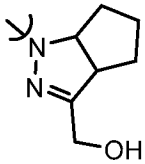
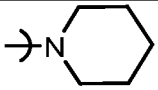
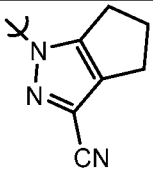
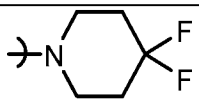
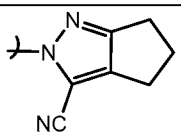
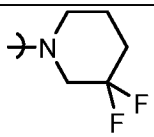
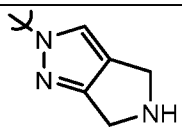
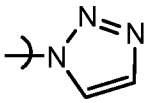
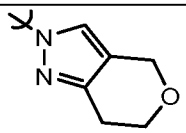
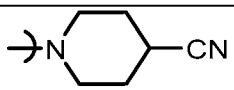
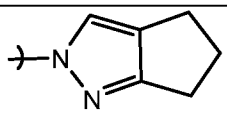
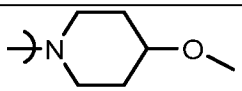
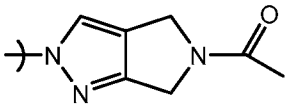
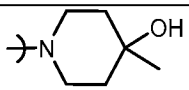
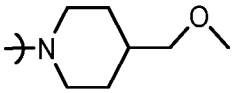
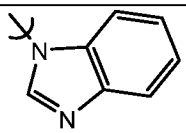
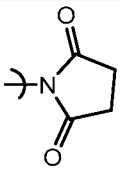
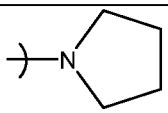
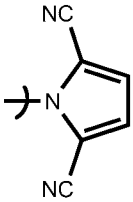
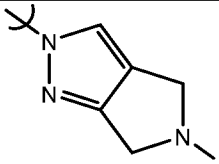
The following Formula (1F1) compounds (para/para; bis) described in Table 9 were prepared in accordance with the schemes and examples described herein. Rings A and B are as described herein.

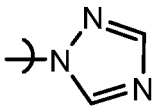
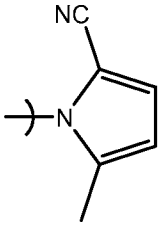
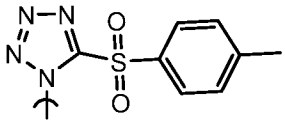
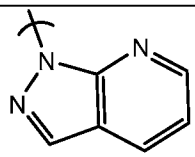
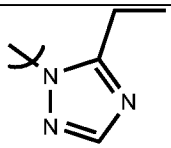
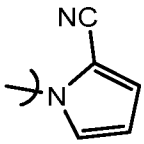
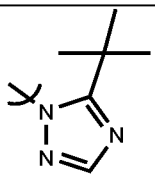
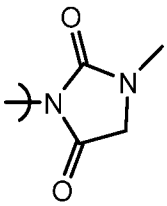
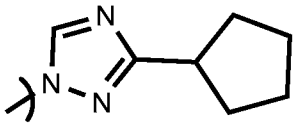
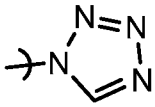
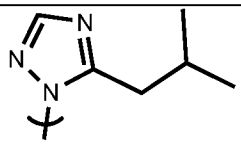
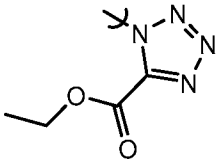
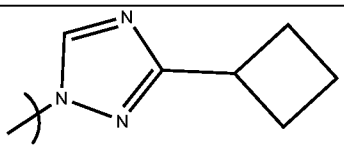
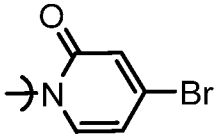
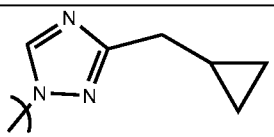
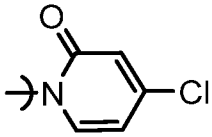
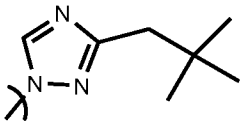


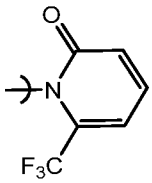
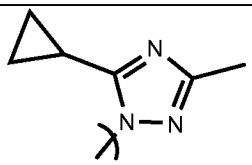
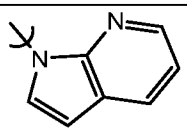
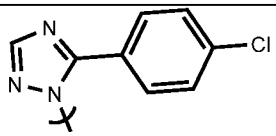
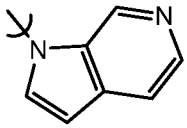
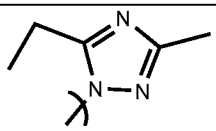
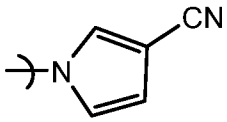
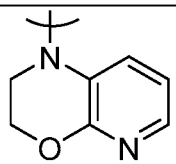
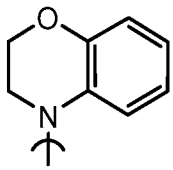
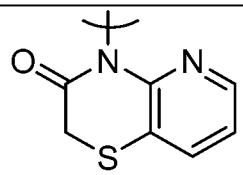
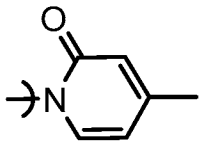
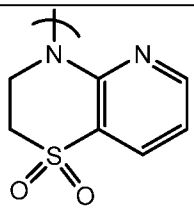
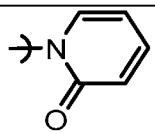
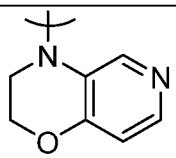
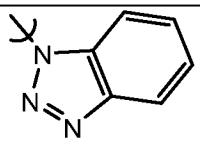
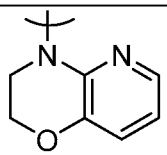
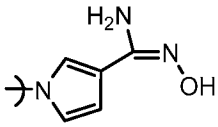
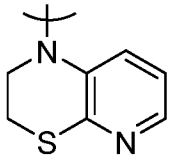
(1F1)

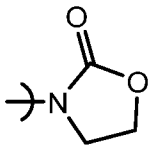
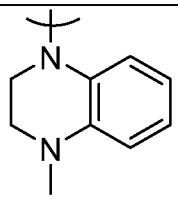
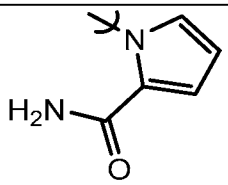
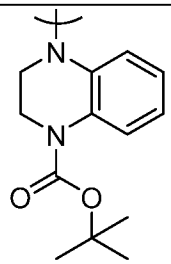
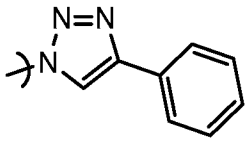
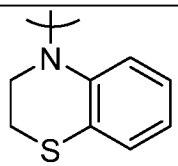
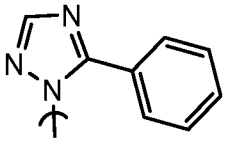
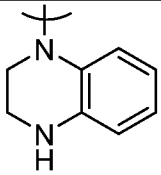
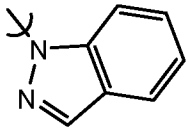
Table 9. Formula (1F1) Symmetrical Compounds

Ex.#	Ring A / Ring B		Ex.#	Ring A / Ring B
9-1			9-36	

9-2			9-37	
9-3			9-38	
9-4			9-39	
9-5			9-40	
9-6			9-41	
9-7			9-42	
9-8			9-43	
9-9			9-44	No example
9-10			9-45	
9-11			9-46	
9-12			9-47	

9-13			9-48	
9-14			9-49	
9-15	No example		9-50	
9-16			9-51	
9-17			9-52	
9-18			9-53	
9-19			9-54	
9-20			9-55	
9-21			9-56	

9-22			9-57	
9-23			9-58	
9-24			9-59	
9-25			9-60	
9-26			9-61	
9-27			9-62	
9-28			9-63	
9-29			9-64	
9-30			9-65	

9-31			9-66	
9-32			9-67	
9-33			9-68	
9-34			9-69	
9-35				

The following Formula (1F1) compound names and example #'s refer to those compounds depicted in Table 9. In one aspect of the invention are Formula (1F1) compounds selected from:

(9-1). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-(morpholinomethyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1148);

(9-2). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-(thiomorpholinomethyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1180);

(9-3). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-(piperidin-1-ylmethyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1144);

(9-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4,4-difluoropiperidin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1215);
(9-5) (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-(3,3-difluoropiperidin-1-yl)benzyl)-18-(4-((3,3-difluoropiperidin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1215);
(9-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1H-1,2,3-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1111);
(9-7). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(piperidine-4-carbonitrile) (1194);
(9-8). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-methoxypiperidin-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1204);
(9-9). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-hydroxy-4-methylpiperidin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1204);
(9-10). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((4-(methoxymethyl)piperidin-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1232);
(9-11) (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2,5-dioxopyrrolidin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1171);
(9-12). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-pyrrole-2,5-dicarbonitrile) (1207);
(9-13). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-(1,2,4-triazol-1-ylmethyl)phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1112);

(9-14). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-tosyl-1H-tetrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1422);
(9-15). No example;
(9-16). 1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[(2-cyanopyrrol-1-yl)methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrrole-2-carbonitrile (1157);
(9-17). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[[(3-methyl-2,5-dioxo-imidazolidin-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1201);
(9-18). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1H-tetrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1113);
(9-19). diethyl 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1H-tetrazole-5-carboxylate) (1257);
(9-20). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-bromo-2-oxopyridin-1(2H)-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1321);
(9-21). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-chloro-2-oxopyridin-1(2H)-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1232);
(9-22). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((2-oxo-5-(trifluoromethyl)pyridin-1(2H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1299);
(9-23). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1H-pyrrolo[2,3-b]pyridin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1209);

(9-24). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1H-pyrrolo[2,3-c]pyridin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1209);
(9-25). 1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[(3-cyanopyrrol-1-yl)methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrrole-3-carbonitrile (1057);
(9-26). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1244);
(9-27). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-methyl-2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1191);
(9-28). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1163);
(9-29). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1211);
(9-30). N'-hydroxy-1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[[2-[(Z)-N'-hydroxycarbamimidoyl]pyrrol-1-yl]methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrrole-2-carboxamidine (1223);
(9-31). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((2-oxooxazolidin-3-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1147);
(9-32). 1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[(2-carbamoylpyrrol-1-yl)methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrrole-2-carboxamide (1215);
(9-33). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)benzyl)-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1106);
(9-34). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-phenyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1264);
(9-35). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2H-indazol-2-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1209);
(9-36). di-tert-butyl 2,2'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate) (1392);
(9-37). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-(hydroxymethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1250);
(9-38). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carbonitrile) (1240);
(9-39). 2-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-(4-((3-cyano-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)methyl)benzyl)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carbonitrile (1240);
(9-40). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1191);
(9-41). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((6,7-dihydropyrano[4,3-c]pyrazol-2(4H)-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-

hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1221);

(9-42) (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-(5,6-dihydro-4H-cyclopenta[c]pyrazol-2-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1188);

(9-43). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(5-acetyl-4,6-dihydropyrrolo[3,4-c]pyrazol-2-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1276);

(9-44). No example.

(9-45). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1H-benzo[d]imidazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1209);

(9-46). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-(pyrrolidin-1-ylmethyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1115);

(9-47). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-methyl-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1220);

(9-48). 1,1'-(((((2R,5S,8R,11S,14R,17S,20R,23S)-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosane-2,14-diyl)bis(methylene))bis(4,1-phenylene))bis(methylene))bis(5-methyl-1H-pyrrole-2-carbonitrile) (1185);

(9-49). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1H-pyrazolo[3,4-b]pyridin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1211);

(9-50). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1167);

(9-51). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(tert-butyl)-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1224);

(9-52). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopentyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1248);

(9-53). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-isobutyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1224);

(9-54). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclobutyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1220);

(9-55). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(cyclopropylmethyl)-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1220);

(9-56). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-neopentyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1252);

(9-57). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopropyl-3-methyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1220);

(9-58). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(4-chlorophenyl)-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1332);

(9-59). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethyl-3-methyl-1H-1,2,4-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1196);

(9-60). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-(2,3-dihydropyrido[2,3-b][1,4]oxazin-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-

hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1244);

(9-61). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-[(3-oxopyrido[3,2-b][1,4]thiazin-4-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1306);

(9-62). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1,1-dioxido-2,3-dihydro-4H-pyrido[3,2-b][1,4]thiazin-4-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1338);

(9-63). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-(2,3-dihydropyrido[4,3-b][1,4]oxazin-4-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1246);

(9-64). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-(2,3-dihydropyrido[3,2-b][1,4]oxazin-4-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1244);

(9-65). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-(2,3-dihydropyrido[2,3-b][1,4]thiazin-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1276);

(9-66). (3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-[(4-methyl-2,3-dihydroquinoxalin-1-yl)methyl]phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1269);

(9-67). tert-butyl 4-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-[[4-[(4-tert-butoxycarbonyl-2,3-dihydroquinoxalin-1-yl)methyl]phenyl]methyl]-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]-2,3-dihydroquinoxaline-1-carboxylate (1440);

(9-68). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-

hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1276); and

(9-69). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-(3,4-dihydro-2H-quinoxalin-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone dihydrochloride (1240).

Table 9'. Formula (1F1) Table 9 Compound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

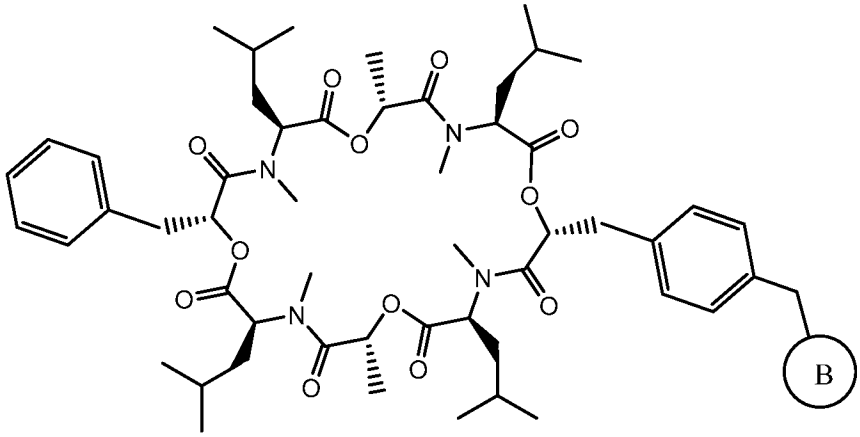
Example	NMR
9-1	0.67-0.94 (m, 26H), 1.16-1.76 (m, 16H), 2.37-3.22 (m, 24H), 3.46-3.60 (m, 4H), 3.65-3.82 (m, 8H), 4.44-5.75 (m, 8 H), 7.14-7.37 (m, 8H)
9-2	1H NMR (400 MHz, CDCl3) δ 0.78-1.10 (m, 30H), 1.20-1.78 (m, 12H), 2.55-3.20 (m, 32H), 3.46 (s, 4H), 4.40-4.50 (m, 1H), 5.00-5.78 (m, 7H), 7.10-7.40 (m, 8H)
9-6	0.6-1.0 (m, 29H), 1.1-1.8 (m, 17 H), 2.6-3.1 (m, 17 H), 4.35-4.45 (m, 0.5H), 5.0-5.75 (m, 12 H), 7.2-7.35 (8H), 7.73 (s, 2H), 8.14 (s, 2H).
9-11	0.6-1.0 (m, 28H), 1.1-1.8 (m, 16 H), 2.65-3.15 (m, 24 H), 4.3-4.5 (m, 1H), 4.51 (s, 4H), 4.4-4.45 (m, 0.6H), 5.0-5.8 (m, 7.4 H), 7.15-7.30 (m, 8H).
9-12	0.69 - 0.96 (m, 28 H), 1.23 - 1.71 (m, 14 H), 2.66 - 3.09 (m, 16 H), 4.40 - 4.45 (m, 1 H), 5.09 - 5.71 (m, 11 H), 7.05 - 7.11 (m, 4 H), 7.21 (s, 4 H), 7.36 - 7.39 (m, 4 H)
9-13	0.64-0.94 (m, 26H), 1.18-1.76 (m, 16 H), 2.67-3.07 (m, 16 H), 4.39-5.73 (m, 12 H), 7.28-7.37 (m, 8H), 8.78-8.82 (m, 4H)
9-14	0.6-1.0 (m, 28H), 1.1-1.8 (m, 14 H), 2.44 (s, 6H), 2.6-3.0 (m, 13 H), 3.0-3.1 (m, 3H), 4.3-4.5 (m, 0.7H), 5.0-5.8 (m, 8 H), 5.96 (s, 4H), 7.23 (d, 4H), 7.35 (d, 4H), 7.52 (d, 4H), 7.90 (d, 4H).
9-16	0.67 - 1.04 (m, 26 H), 1.16 - 1.80 (m, 16 H), 2.62 - 2.96 (m, 13 H), 2.99 - 3.13 (m, 3 H), 4.32 - 4.49 (m, 1 H), 4.96 - 5.75 (m, 11 H), 6.16 - 6.28 (m, 2 H), 6.88 - 7.00 (m, 2 H), 7.05 - 7.18 (m, 4 H), 7.24 - 7.42 (m, 6 H)
9-17	0.65 – 0.98 (m, 26 H) 1.14 - 1.78 (m, 16 H) 2.63 – 2.95 (m, 19 H) 2.99 – 3.10 (m, 3 H) 3.98-4.04 (m,4H) 4.39 – 4.47 (m, 1H) 4.50 (s,4H) 4.99-5.77 (m, 7H) 7.14-7.34 (m, 8H)
9-18	0.6-1.0 (m, 28H), 1.1-1.8 (m, 14 H), 2.6-3.1 (m, 16H), 4.3-4.5 (m, 0.6H), 5.0-5.8 (m, 11.4 H), 7.25- 7.40 (m, 8H).
9-19	0.6-1.0 (m, 30H), 1.1-1.8 (m, 18 H), 2.6-3.1 (m, 16H), 4.3-4.5 (m, 4.5H), 4.95-6.0 (m, 12.6 H), 7.25-7.40 (m, 8H).
9-20	0.61 - 0.99 (m, 26 H) 1.13 - 1.75 (m, 16 H) 2.64 - 3.11 (m, 16 H) 4.37 - 4.46 (m, 1 H) 4.98 - 5.76 (m, 11 H) 6.47 (br d, J=7.34 Hz, 2 H) 6.69 - 6.78 (m, 2 H) 7.21 - 7.33 (m, 8 H) 7.73 - 7.81 (m, 2 H)
9-21	0.63 - 0.99 (m, 26 H) 1.13 - 1.75 (m, 16 H) 2.64 - 3.10 (m, 16 H) 4.36 - 4.48 (m, 1 H) 4.96 - 5.76 (m, 11 H) 6.38 (br d, J=7.34 Hz, 2 H) 6.52 - 6.60 (m, 2 H) 7.23 - 7.35 (m, 8 H) 7.82 - 7.92 (m, 2 H)
9-22	0.57 - 1.00 (m, 26 H) 1.10 - 1.80 (m, 16 H) 2.61 - 3.13 (m, 16 H) 4.32 - 4.49 (m, 1 H) 4.98 - 5.78 (m, 11 H) 6.51 - 6.62 (m, 2 H) 7.24 - 7.37 (m, 8 H) 7.62 - 7.74 (m, 2 H) 8.45 - 8.55 (m, 2 H)
9-23	0.50 - 1.04 (m, 27 H) 1.05 - 1.82 (m, 15 H) 2.57 - 3.10 (m, 16 H) 4.29 - 4.45 (m, 1 H) 4.90 - 5.74 (m, 7 H) 5.84 - 6.09 (m, 4 H) 6.87 - 7.07 (m, 2 H) 7.30 - 7.52 (m, 8 H) 7.57 - 7.79 (m, 2 H) 7.92 - 8.07 (m, 2 H) 8.62 - 8.88 (m, 4 H) 13.52 - 13.68 (m, 2 H)
9-24	0.55 - 1.02 (m, 27 H) 1.05 - 1.77 (m, 15 H) 2.57 - 3.12 (m, 16 H) 4.35 - 4.49 (m, 1 H) 4.94 - 5.59 (m, 6 H) 5.62 - 5.74 (m, 1 H) 5.74 - 5.87 (m, 4 H) 6.85 - 7.04 (m, 2

	H) 7.27 - 7.44 (m, 4 H) 7.44 - 7.54 (m, 4 H) 8.02 - 8.22 (m, 2 H) 8.27 - 8.39 (m, 2 H) 8.39 - 8.57 (m, 2 H) 9.38 - 9.52 (m, 2 H) 12.97 - 13.13 (m, 2 H)
9-25	0.64 - 0.99 (m, 26 H) 1.14 - 1.76 (m, 16 H) 2.63 - 2.95 (m, 13 H) 2.96 - 3.13 (m, 3 H) 4.41 (m, 1 H) 4.98 - 5.76 (m, 11 H) 6.41 - 6.54 (m, 2 H) 6.92 - 7.05 (m, 2 H) 7.17 - 7.38 (m, 8 H) 7.60 - 7.73 (m, 2 H)
9-26	0.67 - 1.01 (m, 27 H), 1.17 - 1.76 (m, 15 H), 2.63 - 3.09 (m, 16 H), 3.30 – 3.33 (m, 4 H), 4.16 – 4.23 (m, 4 H), 4.30 – 4.45 (m, 5 H), 4.94 - 5.74 (m, 7 H), 6.45 - 6.55 (m, 2 H), 6.55 - 6.72 (m, 6 H), 7.19 - 7.32 (m, 8 H)
9-27	0.62 - 0.99 (m, 26 H) 1.13 - 1.78 (m, 16 H) 2.04 - 2.15 (m, 6 H) 2.64 - 3.11 (m, 16 H) 4.35 - 4.49 (m, 1 H) 4.96 - 5.75 (m, 11 H) 6.04 - 6.11 (m, 2 H) 6.21 (s, 2 H) 7.19 - 7.31 (m, 8 H) 7.56 - 7.63 (m, 2 H)
9-28	0.6-1.0 (m, 32H), 1.1-1.8 (m, 20 H), 2.6-3.1 (m, 16 H), 4.3-4.5 (m, 1H), 5.0-5.75 (m, 13 H), 6.15-6.25 (m, 2H), 6.38 (d, 2H), 7.2-7.3 (8H), 7.35-7.45 (m, 2H), 7.7-7.75 (m, 2H).
9-29	0.6-1.0 (m, 33H), 1.1-1.8 (m, 25 H), 2.6-3.1 (m, 16 H), 4.3-4.6 (m, 0.6H), 4.95-5.75 (m, 6.8 H), 5.94 (s, 4H), 7.28 (s, 8H), 7.35-7.45 (m, 2H), 7.45-7.55 (m, 2H), 7.79 (d, 2H), 8.03 (d, 2H).
9-30	0.64 - 0.99 (m, 26 H), 1.16 - 1.79 (m, 16 H), 2.65 - 3.17 (m, 16 H), 4.34 - 4.51 (m, 1 H), 4.93 - 5.74 (m, 11 H), 6.18 - 6.34 (m, 2 H), 6.61 - 6.79 (m, 2 H), 6.91 - 7.42 (m, 10 H)
9-31	0.62 - 1.03 (m, 26 H) 1.06 - 1.92 (m, 20 H) 2.60 - 3.00 (m, 16 H) 3.38 (m 4 H) 4.14 - 4.37 (m, 4 H) 4.91 - 5.90 (m, 8 H) 7.10 - 7.51 (m, 8 H)
9-32	0.62 - 0.96 (m, 26 H), 1.15 - 1.78 (m, 16 H), 2.64 - 2.92 (m, 13 H), 2.96 - 3.08 (m, 3 H), 4.34 - 4.50 (m, 1 H), 4.95 - 5.75 (m, 11 H), 5.98 - 6.11 (m, 2 H), 6.68 - 7.12 (m, 8 H), 7.21 (m, 4 H), 7.33 - 7.57 (m, 2 H)
9-33	0.62 - 0.99 (m, 26 H) 1.06 - 1.81 (m, 16 H) 2.61 - 3.14 (m, 16 H) 4.36 - 4.49 (m, 1 H) 4.97 - 5.78 (m, 9 H) 7.20 - 7.37 (m, 10 H) 7.39 - 7.48 (m, 2 H) 7.78 - 7.88 (m, 2 H) 8.57 - 8.63 (m, 1 H)
9-34	0.68-0.96 (m, 26 H), 1.18-1.76 (m, 16 H), 2.67-3.08 (m, 16 H), 4.40-5.71 (m, 12 H), 7.02 (d, 4 H), 7.28-7.32 (m, 4 H), 7.48-7.56 (m 6 H), 7.62-7.65 (m 4 H), 8.11-8.13 (m, 2 H)
9-35	0.66-0.96 (m, 26 H), 1.20-1.76 (m, 16 H), 2.62-3.07 (m, 16 H), 4.40-5.71 (m, 12 H), 7.02 (d, 4 H), 7.28-7.32 (m, 4 H), 7.48-7.56 (m 6 H), 7.62-7.65 (m 4 H), 8.11-8.13 (m, 2 H)
9-36	0.71 - 0.93 (m, 24 H), 1.17 - 1.67 (m, 33 H), 2.67 - 3.04 (m, 16 H), 4.12 - 4.42 (m, 9 H), 5.03 - 5.68 (m, 14 H), 7.16 - 7.19 (m, 4 H), 7.25 - 7.31 (m, 6 H)
9-37	0.71 - 0.98 (m, 24 H), 1.22 - 1.33 (m, 6 H), 1.36 - 1.51 (m, 3 H), 1.52 - 1.78 (m, 4 H), 2.43 (br d, 4 H), 2.49 - 2.54 (m, 8 H), 2.70 (s, 2 H), 2.78 (d, 4 H), 2.86 - 2.97 (m, 6 H), 3.05 (br s, 3 H), 4.33 (s, 4 H), 4.40 - 4.53 (m, 1 H), 4.94 (br s, 1 H), 4.99 - 5.09 (m, 1 H), 5.10 - 5.30 (m, 8 H), 5.30 - 5.58 (m, 6 H), 5.60 - 5.87 (m, 3 H), 7.16 (d, 4 H), 7.30 (br d, 4 H)
9-39	0.62 - 0.96 (m, 26 H), 1.08 - 1.75 (m, 16 H), 2.20 - 3.04 (m, 30 H), 4.34 - 4.44 (m, 1 H), 4.97 - 5.15 (m, 3 H), 5.17 - 5.44 (m, 5 H), 5.45 - 5.57 (m, 1 H), 5.61 - 5.73 (m, 1 H), 7.02 - 7.43 (m, 1 H), 7.11 - 7.33 (m, 6 H)
9-40	0.72 - 0.94 (m, 24 H), 1.18 - 1.72 (m, 18 H), 2.68 - 3.05 (m, 16 H), 4.14 - 4.20 (m, 8 H), 4.41-4.44 (m, 1 H), 4.98-5.74 (m, 11 H), 7.22-7.32 (m, 10H), 10.11 (brs, 4 H)
9-41	0.53 - 1.07 (m, 26 H) 1.04 - 1.89 (m, 16 H) 2.54 - 3.15 (m, 20 H) 4.41 (m, 1 H) 4.54 (m, 4 H) 4.90 - 5.83 (m, 12 H) 6.82 - 7.40 (m, 8 H) 7.47 (m, 2 H)
9-42	0.68 - 0.94 (m, 26 H), 1.20 - 1.77 (m, 18 H), 2.26 - 2.43 (m, 6 H), 2.67 - 3.03 (m, 18 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.71 (m, 13 H), 7.09 - 7.34 (m, 10 H)
9-43	0.68 - 0.94 (m, 27 H), 1.20 - 1.70 (m, 15 H), 1.97 (s, 6 H), 2.67 - 3.04 (m, 16 H), 4.17 - 4.31 (m, 4 H), 4.33 - 4.44 (m, 1 H), 4.47 - 4.55 (m, 4 H), 5.02 - 5.69 (m, 11 H), 7.16 - 7.19 (m, 4 H), 7.26 -7.30 (m, 6 H)
9-45	0.6-1.0 (m, 28H), 1.1-1.8 (m, 15 H), 2.6-3.1 (m, 16 H), 4.3-4.5 (m, 0.6H), 4.95-5.75 (m, 11 H), 7.15-7.3 (12H), 7.4-7.5 (m, 2H), 7.6-7.7 (m, 2H).
9-46	0.6-1.0 (m, 29H), 1.1-1.8 (m, 26 H), 2.35-2.45 (m, 8H), 2.6-3.1 (m, 20 H), 4.4-4.5 (m, 1H), 4.95-5.75 (m, 8 H), 7.2-7.3 (8H), 8.26 (s, 2H).
9-47	0.74 - 0.94 (m, 28 H), 1.27 - 1.90 (m, 14 H), 2.41 (s, 6 H), 2.67 - 3.04 (m, 16 H), 3.50-3.57 (m, 8 H), 4.40-4.45 (m, 1H), 5.01 - 5.69 (m, 11 H), 7.13 - 7.29 (m, 10 H)

9-48	0.69 - 0.93 (m, 26 H), 1.28 - 1.68 (m, 16 H), 2.16 (s, 6 H), 2.66 - 3.04 (m, 16 H), 4.35 - 4.42 (m, 1 H), 4.9 - 5.68 (m, 11 H), 6.05 (s, 2 H), 6.94 - 6.95 (m, 6 H), 7.31 - 7.32 (m, 4 H)
9-49	0.60 - 0.89 (m, 26 H), 1.01 - 1.77 (m, 16 H), 2.65 - 3.01 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.05 - 5.67 (m, 11 H), 7.15 - 7.24 (m, 10 H), 8.18 (d, J = 2.4 Hz, 2H), 8.26 (d, J = 8.0 Hz, 2H), 8.56 (d, J = 4.3 Hz, 2H)
9-50	0.68-0.95 (m, 26 H), 1.12-1.75 (m, 22 H), 2.67-3.08 (m, 20 H), 4.39-5.71 (m, 12 H), 7.13 (d, 4 H), 7.28-7.32 (m, 4 H), 7.91-7.93 (m, 2 H)
9-51	0.70-0.94 (m, 26 H), 1.21-1.75 (m, 34 H), 2.67-3.08 (m, 16 H), 4.39-5.69 (m, 12 H), 7.03 (d, 4 H), 7.27-7.31 (m, 4 H), 7.86-7.88 (m, 2 H)
9-52	0.68-0.94 (m, 26 H), 1.20-1.90 (m, 32 H), 2.67-3.07 (m, 16 H), 3.28-3.36 (m, 2 H), 4.39-5.70 (m, 12 H), 7.13 (d, 4 H), 7.28-7.32 (m, 4 H), 7.87-7.89 (m, 2 H)
9-53	0.68-0.95 (m, 38 H), 1.20-1.75 (m, 16 H), 1.95-2.04 (m, 2 H), 2.63-3.08 (m, 20 H), 4.39-5.70 (m, 12 H), 7.14 (d, 4 H), 7.28-7.31 (m, 4 H), 7.95 (s, 2 H)
9-54	0.68-0.94 (m, 26 H), 1.19-2.02 (m, 20 H), 2.16-2.26 (m, 8 H), 2.66-3.07 (m, 16 H), 3.71-3.80 (m, 2 H), 4.39-5.70 (m, 12 H), 7.10 (d, 4 H), 7.29 (d, 4 H), 7.92-7.94 (m, 2 H)
9-55	0.12-0.17 (m, 4 H), 0.38-44 (m, 4 H), 0.68-1.04 (m, 28 H), 1.20-1.75 (m, 16 H), 2.66-3.07 (m, 20 H), 4.39-5.70 (m, 12 H), 7.13 (d, 4 H), 7.29 (d, 4 H), 7.91 (s, 2 H)
9-56	0.69-1.02 (m, 44 H), 1.20-1.75 (m, 16 H), 2.67-3.07 (m, 20 H), 4.39-5.70 (m, 12 H), 7.15 (d, 4 H), 7.29 (d, 4 H), 7.90-7.92 (m, 2 H)
9-57	0.68-1.05 (m, 34 H), 1.20-1.76 (m, 16 H), 2.15-2.25 (m, 8 H), 2.68-3.08 (m, 16 H), 4.39-5.72 (m, 12 H), 7.19 (d, 4 H), 7.31 (d, 4 H)
9-58	0.64-0.93 (m, 26 H), 1.16-1.72 (m, 16 H), 2.67-3.07 (m, 16 H), 4.38-5.70 (m, 12 H), 7.02 (d, 4 H), 7.27 (d, 4 H), 7.58 (d, 4 H), 7.68 (d, 4 H), 8.12 (s, 2 H)
9-59	0.68-0.95 (m, 26 H), 1.13-1.75 (m, 22 H), 2.24 (s, 6 H), 2.67-3.08 (m, 20 H), 4.39-5.71 (m, 12 H), 7.17 (d, 4 H), 7.31 (d, 4 H)
9-60	0.71 - 0.92 (m, 23 H), 1.23 - 1.68 (m, 19 H), 2.67 - 3.06 (m, 16 H), 3.40 - 3.50 (m, 4 H), 4.33 - 4.61 (m, 5 H), 5.01 - 5.84 (m, 11 H), 6.72 - 6.89 (m, 2 H), 7.24 - 7.43 (m, 11 H), 7.91 - 7.93 (m, 1 H)
9-61	0.62 - 0.90 (m, 23 H), 1.23 - 1.83 (m, 19 H), 2.65 - 3.18 (m, 16 H), 3.69 (s, 4 H), 4.30 - 4.50 (m, 1 H), 5.01 - 5.84 (m, 11 H), 7.01 - 7.17 (m, 10 H), 8.15 - 8.17 (m, 2 H), 8.17 - 8.18 (m, 2 H)
9-62	0.70 - 0.94 (m, 24 H), 1.20 - 1.90 (m, 18 H), 2.67 - 3.03 (m, 16 H), 3.60 (bs, 4 H), 3.97 (bs, 4 H), 4.35 - 4.45 (m, 1 H), 4.66 (bs, 4 H), 5.03 - 5.68 (m, 7 H), 6.71 - 6.77 (m, 4 H), 7.21 - 7.28 (m, 10 H), 7.59 - 7.61 (m, 2 H)
9-63	0.72 - 0.98 (m, 26 H), 1.24 - 1.75 (m, 16 H), 2.67 - 3.20 (m, 16 H), 3.34 - 3.42 (m, 4 H), 4.36 - 4.48 (m, 4 H), 5.06 - 5.85 (m, 12 H), 7.15 - 7.60 (m, 10 H), 8.10 - 8.30 (m, 4 H)
9-64	0.65 - 0.98 (m, 27 H), 1.20 - 1.80 (m, 15 H), 2.65 - 3.10 (m, 18 H), 3.40 - 3.56 (m, 2 H), 3.80 - 3.88 (m, 2 H), 4.10 - 4.23 (m, 2 H), 4.40 - 4.43 (m, 1 H), 4.76 (bs, 2 H), 4.99 - 5.78 (m, 9 H), 6.18 - 6.22 (m, 1 H), 6.47 - 6.52 (m, 1 H), 6.85 - 6.95 (m, 2 H), 7.20 - 7.36 (m, 8 H), 7.58 - 7.65 (m, 2H)
9-65	0.68 - 1.09 (m, 26 H), 1.20 - 1.80 (m, 16 H), 2.60 - 3.15 (m, 16 H), 3.18 - 3.26 (m, 4 H), 3.54 - 3.59 (m, 4 H), 4.34 - 4.42 (m, 1 H), 5.00 - 5.74 (m, 11 H), 7.15 - 7.80 (m, 12 H), 8.32 - 8.41 (m, 2 H)
9-66	0.70 - 0.94 (m, 26 H), 1.23 - 1.70 (m, 16 H), 2.73 - 3.02 (m, 22 H), 3.22 (bs, 4 H), 3.43 - 3.44 (m, 4H), 4.42 - 4.44 (m, 5 H), 5.01 - 5.69 (m, 7 H), 6.30 - 6.32 (m, 2 H), 6.41 - 6.50 (m, 6 H), 7.18 -7.20 (m, 4 H), 7.24 - 7.26 (m, 4 H)
9-67	0.70 - 0.94 (m, 26 H), 1.23 - 1.69 (m, 34 H), 2.67 - 3.02 (m, 16 H), 3.40 (bs, 4H), 3.72 (bs, 4 H), 4.39 - 4.42 (m, 1 H), 4.50 (s, 4 H), 5.01 - 5.70 (m, 7 H), 6.51 - 6.57 (m, 4 H), 6.80 (t, J = 7.7 Hz, 2 H), 7.17 (d, J = 7.9 Hz, 4 H), 7.26 (d, J = 7.8 Hz, 4 H), 7.32 (d, J = 8.0 Hz, 2 H)
9-68	0.64 - 0.95 (m, 26 H), 1.23 - 1.69 (m, 16 H), 2.67 - 3.08 (m, 20 H), 3.64 - 3.67 (m, 4 H), 4.35 - 4.55 (m, 5 H), 5.0 - 5.7 (m, 7 H), 6.49 - 6.53 (m, 4 H), 6.81 (t, J = 7.8 Hz, 2 H), 6.94 (d, J = 7.5 Hz, 2 H), 7.18 (d, J = 7.9 Hz, 4 H), 7.27 (d, J = 7.9 Hz, 4 H)

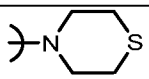
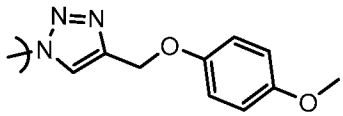
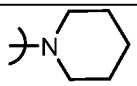
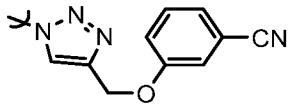
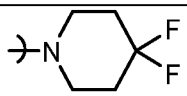
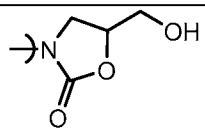
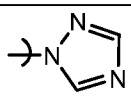
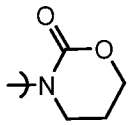
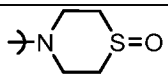
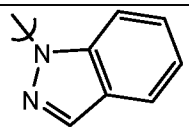
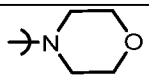
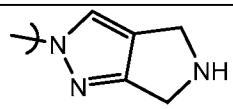
9-69	0.72 - 0.93 (m, 26 H), 1.24 - 1.70 (m, 17 H), 2.67 - 3.03 (m, 16 H), 3.48 - 3.52 (m, 8 H), 4.35 - 4.45 (m, 1 H), 4.50 (bs, 4 H), 5.02 - 5.68 (m, 8 H), 6.62 (bs, 4 H), 6.92 - 7.26 (m, 12 H)

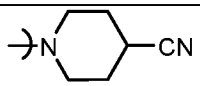
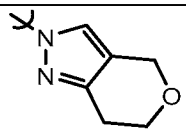
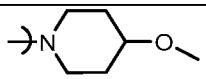
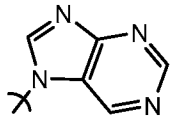
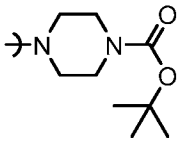
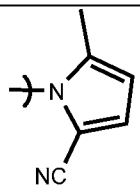
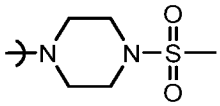
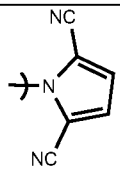
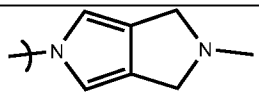
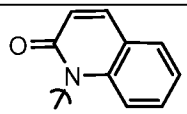
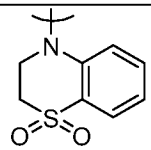
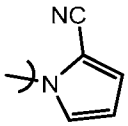
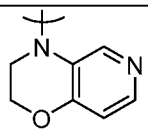
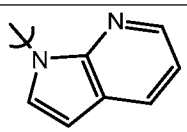
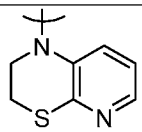
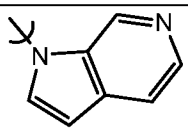
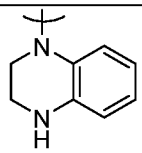
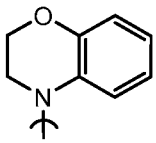
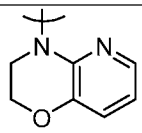
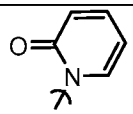
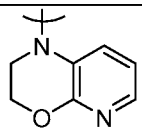
The following Formula (1F2) compounds (hybrid analogs) described in Table 10 were prepared in accordance with the schemes and examples described herein. Ring B is as described herein.

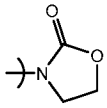
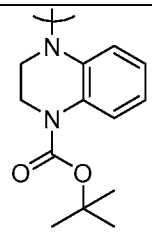
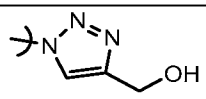
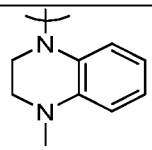
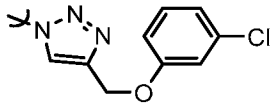
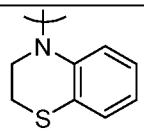
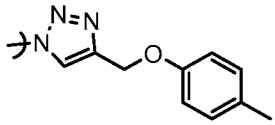


(1F2)

Table 10. Formula (1F2) Compounds

Ex. #	Ring B		Ex. #	Ring B
10-1			10-22	
10-2			10-23	
10-3			10-24	
10-4			10-25	
10-5			10-26	
10-6			10-27	

10-7			10-28	
10-8			10-29	
10-9			10-30	
10-10			10-31	
10-11	No Example		10-32	
10-12			10-33	
10-13			10-34	
10-14			10-35	
10-15			10-36	
10-16			10-37	
10-17			10-38	

10-18			10-39	
10-19			10-40	
10-20			10-41	
10-21				

The following Formula (1F2) compound names and example #'s refer to those compounds depicted in Table 10. In one aspect of the invention, are Formula (1F2) compounds selected from:

(10-1). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-(thiomorpholinomethyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1064);

(10-2). (3S,6R,9S,12R,15S,18S,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-(piperidin-1-ylmethyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1046);

(10-3). (3S,6R,9S,12R,15S,18S,21S,24R)-6-benzyl-18-(4-((4,4-difluoropiperidin-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1082);

(10-4). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-[[4-(1,2,4-triazol-1-ylmethyl)phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1032);

(10-5). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((1-oxidothiomorpholino)methyl)benzyl)-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1080);

(10-6). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-(morpholinomethyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1048);

(10-7). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)piperidine-4-carbonitrile (1071);

(10-8). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-18-(4-((4-methoxypiperidin-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1076);

(10-9). tert-butyl 4-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)piperazine-1-carboxylate (1147);

(10-10). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-(methylsulfonyl)piperazin-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1195);

(10-11). No Example;

(10-12). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((2-oxoquinolin-1(2H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1106);

(10-13). 1-[[4-[[(2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracos-2-yl]methyl]phenyl]methyl]pyrrole-2-carbonitrile (1054);

(10-14). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-pyrrolo[2,3-b]pyridin-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1079);

(10-15). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-pyrrolo[2,3-c]pyridin-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1079);
(10-16). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1096);
(10-17). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((2-oxopyridin-1(2H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1056);
(10-18). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((2-oxooxazolidin-3-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1048);
(10-19). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1060);
(10-20). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((4-((3-chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1171);
(10-21). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-((p-tolyloxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1150);
(10-22). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-18-(4-((4-((4-methoxyphenoxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1166);
(10-23). 3-((1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-

tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)benzonitrile (1161);
(10-24). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((5-(hydroxymethyl)-2-oxooxazolidin-3-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1078);
(10-25). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((2-oxo-1,3-oxazinan-3-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1062);
(10-26). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((1H-indazol-1-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1079);
(10-27). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1070);
(10-28). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((6,7-dihydropyrano[4,3-c]pyrazol-2(4H)-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1085);
(10-29). (3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((7H-purin-7-yl)methyl)benzyl)-18-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1081);
(10-30). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-5-methyl-1H-pyrrole-2-carbonitrile (1067);
(10-31). 1-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-1H-pyrrole-2,5-dicarbonitrile (1078);
(10-32). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((5-methyl-5,6-dihydropyrrolo[3,4-c]pyrazol-

2(4H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1084);

(10-33). (3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((1,1-dioxido-2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1143);

(10-34). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-(2,3-dihydropyrido[4,3-b][1,4]oxazin-4-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1098);

(10-35). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-(2,3-dihydropyrido[2,3-b][1,4]thiazin-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1111);

(10-36). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-(3,4-dihydro-2H-quinoxalin-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone, hydrochloride (1094);

(10-37). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-(2,3-dihydropyrido[3,2-b][1,4]oxazin-4-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1096);

(10-38). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-[[4-(2,3-dihydropyrido[2,3-b][1,4]oxazin-1-ylmethyl)phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone (1096);

(10-39). tert-butyl4-(4-(((2R,5S,8R,11S,14R,17S,20R,23S)-14-benzyl-5,11,17,23-tetraisobutyl-4,8,10,16,20,22-hexamethyl-3,6,9,12,15,18,21,24-octaoxo-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2-yl)methyl)benzyl)-3,4-dihydroquinoxaline-1(2H)-carboxylate (1194);

(10-40). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-18-(4-((4-methyl-3,4-dihydroquinoxalin-1(2H)-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1108); and

(10-41). (3S,6R,9S,12R,15S,18R,21S,24R)-6-benzyl-18-(4-((2,3-dihydro-4H-benzo[b][1,4]thiazin-4-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone (1111).

Table 10'. Formula (1F2) Table 10 Compound NMRs (1H NMR (400Mhz, DMSO-d_6) δ ppm)

Example	NMR
10-1	1H NMR (400 MHz, CDCl3) δ 0.70-1.05 (m, 30 H), 1.30-1.80 (m, 12H), 2.60-3.20 (m, 24H), 3.46 (bs, 2H), 4.40-4.50 (m, 1H), 5.00-5.70 (m, 7H), 7.15-7.32 (m, 9H)
10-4	0.67-0.96 (m, 26H), 1.17-1.74 (m, 16 H), 2.67-3.11 (m, 16 H), 4.39-5.74 (m, 10 H), 7.20-7.37 (m, 9H), 8.82-8.86 (m, 2H)
10-6	0.72-1.11 (m, 26H), 1.16-1.76 (m, 16H), 2.27-2.43 (m, 4H), 2.48-3.15 (m, 16 H), 3.33-3.46 (m, 2H), 3.55-3.68(m, 4H), 3.95-5.94 (m, 8 H), 7.06-7.35 (m, 9H)
10-9	0.57 - 1.04 (m, 26 H) 1.08 - 1.92 (m, 26 H) 2.56 - 3.21 (m, 17 H) 3.28 (br s, 2 H) 4.02 (br s, 2 H) 4.23 - 4.47 (m, 3 H) 4.93 - 5.85 (m, 8 H) 7.12 - 7.55 (m, 9 H)
10-10	0.57 - 1.09 (m, 26 H) 1.09 - 1.85 (m, 16 H) 2.59 - 3.24 (m, 20 H) 3.24 - 3.93 (m, 6 H) 4.18 - 4.54 (m, 3 H) 4.98 - 5.86 (m, 8 H) 7.17 - 7.63 (m, 9 H)
10-11	0.58 - 1.06 (m, 26 H) 1.14 - 1.85 (m, 16 H) 2.62 - 3.40 (m, 22 H) 4.42 (m, 1 H) 4.60 (s, 4 H) 4.85 - 5.91 (m, 8 H) 7.12 - 7.58 (m, 9 H)
10-12	0.51 - 1.02 (m, 26 H) 1.08 - 1.82 (m, 16 H) 2.60 - 3.14 (m, 16 H) 4.31 - 4.48 (m, 1 H) 4.96 - 5.81 (m, 9 H) 6.73 - 6.87 (m, 1 H) 7.08 - 7.18 (m, 2 H) 7.20 - 7.41 (m, 9 H) 7.45 - 7.56 (m, 1 H) 7.84 - 7.90 (m, 1 H) 7.92 - 8.01 (m, 1 H)
10-13	0.63 - 1.03 (m, 26 H), 1.16 - 1.79 (m, 16 H), 2.64 - 2.97 (m, 13 H), 2.99 - 3.13 (m, 3 H), 4.36 - 4.49 (m, 1 H), 4.98 - 5.78 (m, 11 H), 6.17 - 6.29 (m, 1 H), 6.95 (d, J = 3.42 Hz, 1 H), 7.12 (m, 2 H), 7.21 - 7.39 (m, 8 H)
10-14	0.60 - 1.00 (m, 27 H) 1.05 - 1.82 (m, 15 H) 2.57 - 3.14 (m, 16 H) 4.34 - 4.45 (m, 1 H) 4.95 - 5.79 (m, 8 H) 5.84 - 6.05 (m, 2 H) 6.99 - 7.10 (m, 1 H) 7.19 - 7.54 (m, 9 H) 7.62 - 7.75 (m, 1 H) 7.99 (br s, 1 H) 8.70 - 8.83 (m, 2 H) 13.48 - 13.63 (m, 1 H)
10-15	0.57 - 1.04 (m, 27 H) 1.07 - 1.84 (m, 15 H) 2.60 - 3.14 (m, 16 H) 4.35 - 4.49 (m, 1 H) 5.64 (s, 10 H) 6.87 - 6.99 (m, 1 H) 7.15 - 7.54 (m, 9 H) 8.09 - 8.22 (m, 1 H) 8.30 - 8.39 (m, 1 H) 8.42 - 8.52 (m, 1 H) 9.40 - 9.50 (m, 1 H) 12.98 - 13.12 (m, 1 H)
10-16	0.59 - 1.03 (m, 27 H), 1.15 - 1.79 (m, 15 H), 2.63 - 3.15 (m, 16 H), 4.20 (br s, 2 H), 4.36 - 4.48 (m, 3 H), 4.97 - 5.78 (m, 9 H), 6.46 - 6.54 (m, 1 H), 6.57 - 6.62 (m, 1 H), 6.62 - 6.71 (m, 2 H), 7.16 - 7.40 (m, 9 H)
10-17	0.6-1.0 (m, 32H), 1.1-1.8 (m, 20 H), 2.6-3.1 (m, 16 H), 4.3-4.5 (m, 0.85H), 5.0-5.75 (m, 11 H), 6.1-6.2 (m, 1H), 6.3-6.4 (m, 1H), 7.2-7.3 (9H), 7.35-7.45 (m, 1H), 7.7-7.75 (m, 1H).
10-18	0.58 - 1.09 (m, 26 H) 1.12 - 1.90 (m, 16 H) 2.61 - 2.99 (m, 12 H) 3.38 (m, 2 H) 4.15 - 4.49 (m, 4 H) 4.96 - 5.83 (m, 8 H) 7.12 - 7.51 (m, 9 H)
10-19	0.58 - 1.01 (m, 26 H) 1.15 - 1.78 (m, 16 H) 2.64 - 3.13 (m, 16 H) 4.37 - 4.45 (m, 1 H) 4.46 - 4.52 (m, 2 H) 4.98-5.77 (m, 9 H) 7.20 - 7.37 (m, 9 H) 7.92 - 7.98 (m, 1 H)
10-20	0.58 - 1.02 (m, 26 H) 1.13 - 1.79 (m, 16 H) 2.63 - 3.16 (m, 16 H) 4.37 - 4.50 (m, 1 H) 4.96 - 5.79 (m, 11 H) 6.93 - 7.04 (m, 2 H) 7.10 - 7.17 (m, 1 H) 7.21 - 7.39 (m, 9 H) 8.20 - 8.29 (m, 1 H)
10-21	0.62 - 0.99 (m, 26 H) 1.13 - 1.78 (m, 16 H) 2.22 (s, 3 H) 2.64 - 3.14 (m, 16 H) 4.36 - 4.48 (m, 1 H) 4.97 - 5.78 (m, 11 H) 6.84 - 6.94 (m, 2 H) 7.04 - 7.13 (m, 2 H) 7.21 - 7.38 (m, 9 H) 8.17 - 8.24 (m, 1 H)
10-22	0.59 - 0.98 (m, 26 H) 1.06 - 1.82 (m, 16 H) 2.61 - 3.16 (m, 16 H) 3.64 - 3.72 (m, 3 H) 4.35 - 4.51 (m, 1 H) 4.97 - 5.81 (m, 11 H) 6.76 - 6.90 (m, 2 H) 6.90 - 7.03 (m, 2 H) 7.21 - 7.41 (m, 9 H) 8.14 - 8.31 (m, 1 H)
10-23	0.62 - 1.02 (m, 26 H) 1.06 - 1.81 (m, 16 H) 2.62 - 3.15 (m, 16 H) 4.38 - 4.48 (m, 1 H) 4.97 - 5.82 (m, 11 H) 7.18 - 7.59 (m, 13 H) 8.24 - 8.31 (m, 1 H)

10-24	0.61-1.04 (m, 26H), 1.12-1.93 (m, 16H), 2.61-3.25 (m, 15H), 3.32-3.62 (m, 3H), 4.21-4.61 (m, 4H), 4.93-5.82 (m, 8H), 7.10-7.40 (m, 9H)
10-25	0.63-1.02 (m, 24H), 1.12-2.0 (m, 18H), 2.58-3.24 (m, 17H), 4.09-4.28 (m, 2H), 4.33-4.49 (m, 2H), 4.93-5.83 (m, 10H), 7.12-7.49 (m, 9H)
10-26	0.66 – 0.97 (m, 26 H), 1.15 - 1.76 (m, 16 H), 2.64 - 2.95 (m, 13 H), 2.98 - 3.13 (m, 3 H), 4.38 - 5.76 (m, 10 H), 6.99 – 7.03 (m, 1 H), 7.18-7.33 (m, 10 H), 7.56 (d, 1 H), 7.68 (d, 1 H), 8.43 (s, 1 H)
10-27	0.80 - 0.95 (m, 24 H), 1.09 - 1.71 (m, 18 H), 2.68 - 3.06 (m, 16 H), 4.13 - 4.20 (m, 4 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.69 (m, 10 H), 7.21 - 7.30 (m, 9 H), 9.92 (brs, 2 H)
10-28	0.58-1.03 (m, 24H), 1.14-1.86 (m, 16H), 2.55-3.16 (m, 16H), 3.72-3.92 (m, 2H), 4.33-4.50 (m, 1H), 4.50-4.64 (m, 2H), 4.91-5.85 (m, 9H), 6.98-7.63 (m, 10H)
10-29	0.51 - 1.00 (m, 26 H), 1.08 - 1.92 (m, 16 H), 2.58 - 3.22 (m, 16 H), 4.41 (m, 1 H), 4.47 - 4.49 (m, 1 H), 4.91 - 5.96 (m, 10 H) 7.14 - 7.73 (m, 9 H), 9.16 (s, 1 H), 9.68 (s, 1 H), 9.95 (s, 1 H)
10-30	0.68 - 0.95 (m, 26 H), 1.23 - 1.7 (m, 16 H), 2.16 (s, 3 H), 2.66 - 3.31 (m, 16 H), 4.35 - 4.45 (m, 1 H), 5.02 - 5.8 (m, 9 H), 6.05 (d, J = 3.9 Hz, 1 H), 6.91 - 6.95 (m, 2 H), 7.23 - 7.31 (m, 8 H)
10-31	0.68 - 0.96 (m, 26 H), 1.23 - 1.58 (m, 16 H), 2.66 - 3.06 (m, 16 H), 4.40 - 4.42 (m, 1 H), 5.01 - 5.75 (m, 9 H), 7.11 (d, J = 7.9 Hz, 2 H), 7.21 - 7.31 (m, 7 H), 7.36 - 7.40 (m, 2 H)
10-32	0.80 - 0.94 (m, 26 H), 1.34 - 1.85 (m, 16 H), 2.41 (s, 3 H), 2.67 - 3.05 (m, 16 H), 3.50 - 3.57 (m, 4 H), 4.40-4.42 (m, 1 H), 5.11 - 5.69 (m, 9 H), 7.13 - 7.31 (m, 10 H)
10-33	0.70 - 0.94 (m, 24 H), 1.20 - 1.73 (m, 18 H), 2.67 - 3.05 (m, 16 H), 3.60 (bs, 2 H), 3.97 (bs, 2 H), 4.35 - 4.45 (m, 1 H), 4.66 (bs, 2 H), 5.03 - 5.78 (m, 7 H), 6.71 - 6.77 (m, 2 H), 7.21 - 7.30 (m, 10 H), 7.59 - 7.61 (m, 1 H)
10-34	0.60 - 1.00 (m, 26 H), 1.15 - 1.80 (m, 16 H), 2.65 - 3.10 (m, 16 H), 3.30 - 3.41 (m, 2 H), 4.38 - 4.42 (m, 2 H), 5.00 - 5.78 (m, 10 H), 7.19 - 7.48 (m, 10 H), 8.14 - 8.30 (m, 2 H)
10-35	0.65 - 1.03 (m, 27 H), 1.20 - 1.80 (m, 15 H), 2.65 - 3.15 (m, 16 H), 3.18 - 3.28 (m, 2 H), 3.55 - 3.62 (m, 2 H), 4.39 - 4.46 (m, 1 H), 5.00 - 5.80 (m, 9 H), 7.20 - 7.80 (m, 11 H), 8.35 - 8.40 (m, 1 H)
10-36	0.65 - 1.00 (m, 26 H), 1.11 - 1.76 (m, 16 H), 2.65 - 3.10 (m, 16 H), 4.35 - 4.50 (m, 4 H), 5.00 - 5.80 (m, 11 H), 6.50 - 6.90 (m, 4 H), 7.20 -7.38 (m, 9 H)
10-37	0.70 - 0.94 (m, 26 H), 1.27 - 1.68 (m, 16 H), 2.68 - 3.05 (m, 16 H), 4.15 (s, 2 H), 4.40 - 4.43 (m, 1 H), 4.77 - 5.73 (m, 11 H), 6.50 - 6.52 (m, 1 H), 6.95 (d, J = 7.2 Hz, 1 H), 7.19 - 7.31 (m, 9 H), 7.64 - 7.65 (m, 1 H)
10-38	0.68 - 0.95 (m, 26 H), 1.23 - 1.69 (m, 16 H), 2.67 - 3.05 (m, 16 H), 3.31 - 3.37 (m, 2 H), 4.33 - 4.44 (m, 5 H), 5.09 - 5.69 (m, 7 H), 6.71 - 6.74 (m, 1 H), 6.88 - 6.91 (m, 1 H), 7.22 - 7.37 (m, 10 H)
10-39	0.70 - 0.94 (m, 26 H), 1.23 - 1.70 (m, 25 H), 2.67 - 3.05 (m, 16 H), 3.40 (bs, 2 H), 4.42 - 4.50 (m, 3 H), 5.02 - 5.70 (m, 9 H), 6.51 - 6.54 (m, 2 H), 6.80 (bs, 1 H), 7.16 - 7.31 (m, 10 H)
10-40	0.84 - 0.94 (m, 26 H), 1.42 - 1.70 (m, 16 H), 2.67 - 2.95 (m, 16 H), 3.22 (s, 3 H), 3.43-3.44 (2H, m), 4.39 - 4.43 (m, 3 H), 5.02 - 5.73 (m, 9 H), 6.30 - 6.47 (m, 4 H), 7.18 - 7.31 (m, 9 H)
10-41	0.68 - 0.95 (m, 26 H), 1.23 - 1.69 (m, 16 H), 2.67 - 3.09 (m, 18 H), 3.64 - 3.67 (m, 2 H), 4.4 - 4.55 (m, 3 H), 5.0 - 5.75 (m, 7 H), 6.51 - 6.54 (m, 2 H), 6.81 - 6.82 (m, 1 H), 6.93 - 6.95 (m, 1 H), 7.17 - 7.31 (m, 9 H)

Biological

Heartworm infection, caused by the endoparasite *Dirofilaria immitis (D. immitis)*, can be a severe and life-threatening disease in animals such as dogs and cats. Heartworm has a complicated life cycle involving several life stages before they

mature into adults that will eventually infect the pulmonary artery of the host animal. Heartworm transmission also requires the mosquito to act as an intermediate host to complete this life cycle. For example, the beginning of the heartworm life cycle and transmission process involves a mosquito biting a previously infected dog and ingesting blood containing heartworm microfilariae (larva stage 1). Within the mosquito, the microfilariae will molt into infective larva stage 3 (L3) worms over a two week period. Once the mosquito bites another dog, infective L3 worms will move through the bite wound to enter the host and migrate into the tissues where they will begin molting into larva stage 4 (L4) worms, usually within 1 to 3 days post infection. Subsequently, L4 worms will continue their migration through tissues and molt into sexually immature or "adolescent" adults (larva stage 5, immature adult), approximately 50-70 days post infection. Sexually mature worms will eventually migrate to the heart and lungs of the dog, as early as 70 days post infection. Approximately 6-7 months post infection *D. immitis* adults reach maturity and sexually reproduce in the pulmonary artery leading to microfilaria (MF) production and circulation in the blood of the dog, thus completing the heartworm life cycle.

The most commonly used heartworm preventatives are the macrocyclic lactones (MLs) such as ivermectin, moxidectin and selamectin. These agents are administered on a monthly basis whereby they kill *D. immitis* L3 and L4 worms acquired by the host within the previous 30 days. Their primary action is to disrupt the heartworm life cycle by killing L3 and L4 worms thus preventing adult formation and subsequent disease. While very effective at preventing heartworm disease, owners are advised to test dogs for existing heartworm infections (i.e. heartworm positive dogs) prior to starting treatment with MLs due to their potential to kill circulating microfilariae. A rapid decrease in the numbers of microfilariae in the blood can lead to hypersensitivity-type reactions and circulatory shock (e.g. anaphylaxis), presumably due to dead or dying microfilariae. These potential adverse effects can be life-threatening to the dog and as such are presented as caution statements on many ML product labels. Therefore, the discovery of a novel heartworm preventative that would selectively target L3 and L4 stage worms versus microfilariae would offer a potential safety advantage. By not killing circulating microfilariae in heartworm positive dogs, a targeted treatment would prevent the adverse effects known to occur with other heartworm preventatives that lack *D. immitis* stage selectivity.

To identify novel heartworm preventatives, compounds were screened for nematocidal activity using *in vitro* motility assays. The compounds described herein have demonstrated nematocidal activity against either *Dirofilaria immitis* (Larva stage 4 (*Di*L4)) and/or *Dirofilaria immitis* (microfilaria (*Di*MF)) as determined by reductions in nematode motility either by paralysis or death. Active and selective (*Di*L4 vs. *Di*MF potency) example compounds were subsequently evaluated in heartworm positive dog studies to correlate the *in vitro* selectivity profile with *in vivo* effects on circulating microfilariae.

The *in vitro* (*Di*L4 and *Di*MF) and *in vivo* (heartworm positive dog studies) biological activity against *Dirofilaria immitis* of the compounds of the invention can be measured using the test methods described below.

Dirofilaria immitis, Microfilaria (*Di*MF) *In vitro* Assay

Compounds were dissolved and serially diluted in DMSO. Aliquots were spotted to the empty wells of assay plates. Media and microfilariae of *Dirofilaria immitis* were added to each well to dilute the test compounds to the desired concentrations. Assay plates were incubated for approximately 72 hours, and the larvae in each well were observed microscopically for drug effect. Microfilariae in each well were assessed subjectively for survival or paralysis, and results were reported as Minimum Effective Dose (MED). In accordance with the method described above, the following compounds had DiMF MED ≤1nM: 1a-36, 1a-37, 1b-16, 1b-17, 1b-18, 1b-23, 1b-32, 1b-66, 1b-86, 1b-96, 1b-104, 1b-115, 1b-146, 1b-160, 1b-166, 1b-168, 1b-171, 1b-173, 1b-176, 1b-177, 1b-189, 1b-194, 1b-208, 1b-212, 1c-1, 1c-3, 1c-4, 1c-6, 1c-7, 1c-9, 1c-10, 2-1, 2-30, 6-3, 6-9, 6-15, 8-9, 9-12, 9-16, 9-32, 9-50, 9-54, 9-55, 10-13, and 10-31. The following compounds had DiMF MED >1nM and ≤ 10nM: 1a-1, 1a-2, 1a-7, 1a-10, 1a-11, 1a-16, 1a-17, 1a-20, 1a-21, 1a-24, 1a-38, 1a-46, 1b-7, 1b-8, 1b-10, 1b-19, 1b-21, 1b-24, 1b-25, 1b-29, 1b-35, 1b-46, 1b-52, 1b-62, 1b-70, 1b-89, 1b-94, 1b-95, 1b-103, 1b-105, 1b-108, 1b-118, 1b-119, 1b-121, 1b-126, 1b-135, 1b-142, 1b-143, 1b-145, 1b-150, 1b-151, 1b-152, 1b-154, 1b-155, 1b-165, 1b-174, 1b-175, 1b-184, 1b-190, 1b-197, 1b-201, 1b-203, 1b-205, 1b-207, 1b-211, 1b-213, 1b-215, 1b-216, 1b-220, 1b-221, 1c-2, 1c-5, 1c-11, 1c-12, 2-2, 2-7, 2-10, 2-12, 2-18, 2-19, 2-22, 2-25, 2-28, 2-29, 2-39, 2-41, 2-44, 2-45, 2-46, 2-47, 2-48, 2-51, 2-55, 2-62, 2-65, 2-66, 2-69, 2-74, 2-75, 2-76, 2-77, 2-87, 3-1, 3-2, 3-3, 3-8, 3-11, 3-27, 3-36, 3-37, 3-39, 3-41, 4-1, 4-2, 4-14, 5-1, 5-2, 6-1, 6-12, 6-16, 6-19, 6-20, 7-3,

7-9, 8-3, 8-7, 8-8, 8-12, 8-13, 8-15, 9-1, 9-6, 9-11, 9-21, 9-22, 9-25, 9-28, 9-30, 9-34, 9-41, 9-48, 9-49, 9-51, 9-52, 9-53, 9-56, 10-6, 10-17, 10-30, 10-37, and 10-38. The following compounds had DiMF MED >10 and ≤ 100nM: 1a-3, 1a-6, 1a-8, 1a-12, 1a-13, 1a-14, 1a-15, 1a-18, 1a-19, 1a-22, 1a-23, 1a-25, 1a-26, 1a-28, 1a-29, 1a-30, 1a-31, 1a-32, 1a-33, 1a-35, 1a-39, 1b-4, 1b-5, 1b-12, 1b-13, 1b-15, 1b-20, 1b-22, 1b-31, 1b-34, 1b-38, 1b-39, 1b-43, 1b-45, 1b-53, 1b-54, 1b-58, 1b-63, 1b-64, 1b-67, 1b-69, 1b-71, 1b-75, 1b-87, 1b-91, 1b-97, 1b-106, 1b-110, 1b-111, 1b-112, 1b-113, 1b-116, 1b-117, 1b-120, 1b-124, 1b-127, 1b-128, 1b-129, 1b-133, 1b-138, 1b-139, 1b-140, 1b-141, 1b-144, 1b-149, 1b-156, 1b-159, 1b-162, 1b-163, 1b-169, 1b-170, 1b-172, 1b-180, 1b-181, 1b-183, 1b-185, 1b-186, 1b-187, 1b-188, 1b-191, 1b-195, 1b-198, 1b-199, 1b-206, 1b-209, 1b-210, 1b-214, 1b-217, 1b-218, 1b-219, 1b-222, 2-3, 2-5, 2-8, 2-9, 2-11, 2-13, 2-14, 2-15, 2-16, 2-17, 2-20, 2-21, 2-23, 2-24, 2-26, 2-27, 2-31, 2-32, 2-35, 2-36, 2-38, 2-40, 2-42, 2-43, 2-50, 2-52, 2-54, 2-56, 2-57, 2-58, 2-59, 2-60, 2-61, 2-64, 2-67, 2-68, 2-70, 2-71, 2-72, 2-78, 2-79, 2-81, 2-82, 2-83, 2-84, 2-85, 2-86, 2-88, 3-10, 3-12, 3-13, 3-18, 3-19, 3-20, 3-21, 3-23, 3-24, 3-25, 3-29, 3-38, 3-43, 4-9, 4-15, 4-16, 4-17, 5-3, 5-4, 5-6, 6-2, 6-4, 6-5, 6-6, 6-7, 6-8, 6-10, 6-11, 6-14, 6-18, 7-1, 7-2, 7-4, 7-7, 7-11, 8-2, 8-4, 8-5, 8-6, 8-10, 8-11, 8-14, 9-2, 9-4, 9-5, 9-18, 9-20, 9-27, 9-29, 9-33, 9-35, 9-42, 9-57, 9-58, 9-59, 9-61, 9-62, 9-64, 10-2, 10-3, 10-9, 10-10, 10-11, 10-12, 10-14, 10-16, 10-18, 10-19, 10-21, 10-22, 10-23, 10-24, 10-25, 10-26, 10-27, 10-28, 10-32, 10-33, 10-35, and 10-41.

Dirofilaria immitis, L4 stage (*Di*L4) *In vitro* Assay

Compounds were dissolved and serially diluted in DMSO. Aliquots were spotted to the empty wells of assay plates. Media and 4th stage larvae (L4) of *Dirofilaria immitis* were added to each well to dilute the test compounds to the desired concentrations. Assay plates were incubated for approximately 72 hours, and the larvae in each well were observed microscopically for drug effect. Larvae in each well were assessed subjectively for survival or paralysis, and results were reported as Minimum Effective Dose (MED).). In accordance with the method described above, the following compounds had DiL4 MED ≤ 0.1nM: 1a-7, 1b-15, 1b-66, 1b-89, 1b-96, 1b-115, 1b-119, 1b-154, 1b-166, 1b-171, 1b-176, 1b-177, 1b-211, 1b-216, 1c-1, 1c-2, 1c-3, 1c-6, 1c-7, 1c-8, 1c-10, 1c-11, 6-3, 6-9, 6-12, 9-12, 9-16, 9-48, and 10-31. The following compounds had DiL4 MED > 0.1 and ≤ 1nM: 1a-1, 1a-11, 1a-12, 1a-13, 1a-16, 1a-20, 1a-21, 1a-26, 1a-31, 1a-36, 1a-37, 1b-16, 1b-17, 1b-21, 1b-23,

1b-25, 1b-32, 1b-35, 1b-46, 1b-51, 1b-86, 1b-104, 1b-108, 1b-112, 1b-113, 1b-118, 1b-126, 1b-129, 1b-150, 1b-151, 1b-160, 1b-165, 1b-173, 1b-186, 1b-189, 1b-190, 1b-194, 1b-205, 1b-206, 1b-209, 1b-210, 1b-212, 1b-215, 1b-217, 1b-219, 1b-222, 1c-4, 1c-5, 1c-12, 1c-13, 2-1, 2-10, 2-22, 2-25, 2-28, 2-41, 2-51, 2-55, 2-62, 2-64, 2-66, 2-69, 2-76, 2-77, 3-1, 3-3, 3-18, 3-19, 3-27, 3-36, 3-37, 4-2, 6-15, 7-3, 7-9, 8-3, 8-9, 8-12, 8-15, 9-25, 9-26, 9-32, 9-55, 10-13, 10-30, and 10-38. The following compounds had DiL4 MED >1 to ≤ 10nM: 1a-34, 1a-38, 1a-39, 1b-14, 1b-19, 1b-68,

As a means of assessing the compounds selectivity against *D. immitis* microfilaria and L4 larvae, selectivity was calculated as a ratio (DiMF/DiL4). The following compounds had a DiMF/DiL4 ratio ≥ 10 and < 100: 1a-1, 1a-12, 1a-13, 1a-20, 1a-26, 1a-31, 1a-34, 1b-14, 1b-35, 1b-46, 1b-69, 1b-89, 1b-96, 1b-108, 1b-113, 1b-126, 1b-127, 1b-128, 1b-129, 1b-149, 1b-151, 1b-171, 1b-172, 1b-186, 1b-206, 1b-209, 1b-215, 1b-216, 1b-217, 1b-219, 1c-5, 1c-8, 1c-10, 1c-11, 2-41, 2-55, 2-69, 3-3, 3-18, 3-19, 4-2, 6-12, 9-16, 9-61, 10-31, and 10-38. The following compounds had a DiMF/DiL4 ratio ≥ 100: 1a-7, 1b-15, 1b-51, 1b-68, 1b-112, 1b-119, 1b-153, 1b-154, 1b-178, 1b-210, 1b-222, 1c-2, 1c-3, 1c-11, 1c-13, 2-64, 9-26, 9-48, and 9-63.

Heartworm Positive Dog Studies

Dogs with pre-existing heartworm infections, via surgical transplantation were used for these studies. To confirm that the dogs had circulating microfilariae, blood samples were taken from each dog and examined for microfilariae by using the modified Knott's method. All dog cohorts included in the studies exhibited average microfilariae counts of at least 15,000 MF/mL of the blood (pre-dose). On approximately Day -7, dogs were randomly allocated to treatments (three animals per treatment group) based on Day -7 MF counts. Dogs were fasted overnight prior to dosing and fed immediately following dosing of the test articles. Compounds were administered by point dosing in oral liquid-filled capsules on Day 0. Blood samples were collected to measure MF counts on Days 0 (pre-dose and 2 hours post-dose), 1, 2, 7, 21 and 28. Clinical observations were conducted by a suitably experienced veterinarian on days -7, 0 (immediately prior to treatment, 1-2 hours post-treatment), 1 and 2 whereby any abnormal clinical signs were documented using standard veterinary medical terminology. Additionally, general health observations were conducted throughout the study including (but not limited to) general physical appearance and behavior, abnormalities of food and water consumption,

vomiting/regurgitation, appearance of urine and feces and any sign of MF anaphylaxis.

The reference depsipeptide, emodepside, has equivalent *in vitro* potency against *Di*L4 (30 nM) and *Di*MF (30 nM) when assessed in the nematode motility assays and therefore represents a non-selective compound, i.e., selectivity ratio (*Di*MF/*Di*L4) of 1. Data from this comparison is shown in Table 11. As such, emodepside was evaluated for effects against circulating microfilariae in a heartworm positive dog study. At a dose of 1 mg/kg (po), emodepside demonstrated a rapid killing of circulating microfilariae, reducing the average MF counts from 61,000 MF/mL of blood pre-dose to 8,300 MF/mL of blood at 2 hours post-dose (~86% decrease). Moreover, all treated dogs exhibited adverse effects consistent with dead or dying circulating microfilariae (e.g. lethargy, tremors, ataxia, hyper-salivation) within 2 hours of emodepside administration. All dogs were treated with dexamethasone, epinephrine and valium such that they were able to recover from their symptoms.

In contrast to emodepside, the compounds described herein demonstrate larva stage selectivity (i.e. *Di*L4 vs. *Di*MF potency). As such, two compound examples were progressed into heartworm positive dog studies to correlate the *in vitro* selectivity profile with *in vivo* effects on circulating microfilariae. The DiL4 and DiMF MED for Example 1b-14 was 6nM and 300nM, respectively. For Example 1b-25, the DiL4 and DiMF MED was 0.6nM and 5 nM, respectively. Example 1b-25, which has a selectivity ratio of about 8.3, was dosed up to 3 mg/kg (po) with no significant effects on circulating MF counts out to day 21 post-dose. Additionally, there were no adverse effects observed following the administration of Example 1b-25, consistent with a lack of microfilariae kill in the blood. Similarly, Example 1b-14, which exhibits a selectivity ratio of 50, was dosed at 1 mg/kg (po) with no significant effects on circulating MF counts throughout the dog study. Average mean MF counts were 15,000 MF/mL of blood pre-dose and remained elevated throughout the study where it averaged 28,000 MF/mL of blood on day 21 of the dog study. Moreover, there were no adverse clinical observations noted throughout the study, consistent with a lack of potency against circulating MF in the dogs. These data highlight the importance of generating larva stage selective compounds as novel heartworm preventatives. Specifically targeting the L4 stage versus the MF stage worms provide an improved safety profile when administering preventatives to dogs with an already active adult heartworm infection. Indeed, the compounds described herein

exhibit improved selectivity ratios (i.e. *Di*L4 vs. *Di*MF potency) whereby they offer improved safety over older preventatives and reference depsipeptides such as emodepside.

Table 11. Heartworm positive dog studies evaluating effects on circulating microfilariae (MF) following compound administration.

Compound		Day 0 Pre-dose	Day 0, Post-dose, 2 hours	Day 1	Day 7	Day 14	Day 21
Emodepside	Mean MF/mL	61,000	8,300	4,500	8,800	13,000	13,000
	% Reduction		86%	93%	86%	79%	79%
Example 1b-14	Mean MF/mL	15,000	20,000	14,000	15,000	33,000	28,000
	% Reduction		-33%	7%	0%	-120%	-87%
Example 1b-25	Mean MF/mL	32,000	34,000	26,000	27,000	40,000	46,000
	% Reduction		-6%	19%	16%	-25%	-44%

Microfilariae raw counts are shown as mean MF/mL (3 dogs/treatment) of blood. Percent reductions were calculated from counts on day of assessment compared back with pre-dose (Day 0) levels. Negative percent reductions are a reflection of natural variability across time due to active adult heartworm infection and continued microfilariae production.

Canine pharmacokinetic (PK) data is provided for some Formula (1) compounds that were administered orally or intravenously in Table 12. As can be seen, the compounds have long plasma half-lives and clearance values that are low or moderate. The oral bioavailabity is variable ranging from a low of less than 1% to well absorbed at 78%.

Table 12. Pharmacokinetic Data from Dogs Following a Single IV or Oral Dose Dose of a Formula (1) compound

	Oral 1mg/kg		IV 0.5 or 0.2 mg/kg		
Example #	Cmax (ng/mL)	F (%)	t½ (hrs)	Cl (mL/min/kg)	Vdss (mL/kg)
1b-14	111	10	138	0.9	2700
1b-15	5	0.2	67	0.05	320
1b-19	267	24	87	2.4	7250
1b-21	145	78	36.1	15.5	28400
1b-23	205	34	27	14	8540
1b-25	152	12	110	2	3000
1b-45	127		104*		
1b-68	39	4	163	1	7580
1b-69	27	5	256	1	3810
1b-108	178	30	51	6	5600
9-26	71	1	106	0.1	600

* oral t½

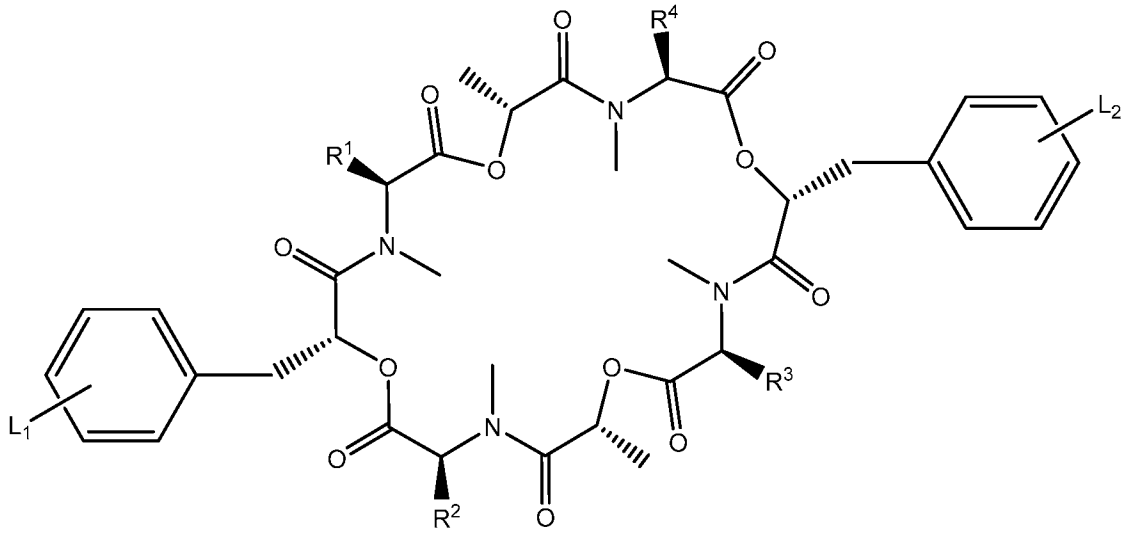
Haemonchus contortus L3 (HcL3) Assay

Compounds were dissolved and serially diluted in DMSO. Aliquots were spotted to the empty wells of assay plates. Media and third stage larvae of Haemonchus contortus were added to each well to dilute the test compounds to the desired concentrations. Assay plates were incubated for approximately 96 hours, and the larvae in each well were observed microscopically for drug effect. Larvae in each well were assessed subjectively for survival or paralysis, and results were reported as Minimum Effective Dose (MED). In accordance with the method described above, the following compounds had an MED ≤ 1μM: 1b-18, 1b-23, 1b-66, 1b-89, 1b-94, 1b-96, 1b-104, 1b-108, 1b-115, 1b-151, 1b-160, 1b-165, 1b-171, 1b-173, 1b-176, 1b-177, 1b-206, 1b-211, 1b-212, 1b-215, 1b-216, 1b-217, 1b-219, 1b-222, 1c-1, 1c-2, 1c-3, 1c-4, 1c-5, 1c-6, 1c-7, 1c-9, 1c-10, 1c-11, 9-12, 9-16, 9-32, 9-48, and 9-55. The following compounds had an MED > 1 and ≤ 10μM: 1a-10, 1a-14, 1a-16, 1a-17, 1a-20, 1a-21, 1a-26, 1a-31, 1a-35, 1a-36, 1a-37, 1b-16, 1b-17, 1b-19, 1b-21, 1b-24, 1b-29, 1b-46, 1b-52, 1b-95, 1b-110, 1b-118, 1b-126, 1b-127, 1b-129, 1b-143, 1b-145, 1b-166, 1b-179, 1b-186, 1b-187, 1b-190, 1b-197, 1b-201, 1b-207, 1b-210, 1b-213, 1b-214, 1b-221, 2-1, 2-2, 2-7, 2-19, 2-22, 2-28, 2-30, 2-45, 2-51, 2-53, 2-66, 2-68, 2-69, 2-74, 2-79, 2-87, 3-1, 3-2, 3-3, 3-27, 6-3, 6-7, 6-9, 6-12, 6-20, 7-9, 8-3, 8-4, 8-6, 8-7, 8-8, 8-9, 8-13, 8-15, 9-1, 9-6, 9-11, 9-22, 9-28, 9-34, 9-41, 9-50, 9-51, 9-52, 9-53, 9-54, 9-56, 9-57, 9-59, 10-3, 10-6, 10-11, 10-13, 10-17, 10-18, 10-30, and 10-31. The following compounds had an MED > 10 and ≤ 100μM: 1b-25, 1b-32, 1b-35, 1b-86, 1b-119, 1b-189, 1b-203, 1b-208, 1b-220, and 9-69.

Claims

We claim

1. A compound of Formula (1)



(1)

wherein

L_1 and L_2 are each individually and separately C_1-C_4alkylheteroaryl and C_1-C_4alkylheterocycle, wherein the heteroaryl moiety is a 5- or 6-member monocyclic aromatic ring or a 8- to 11-member fused aromatic ring each containing at least one heteroatom selected from N, O, and S; and the heterocycle moiety is a 4- to 6-member monocyclic saturated or partially saturated ring or a 8- to 11-member fused saturated or partially saturated ring, and wherein the heteroaryl and heterocycle moiety are N-linked to the alkyl;

and wherein the L_1 and L_2 alkyl moiety of the alkylheteroaryl and alkylheterocycle is optionally substituted with at least one substituent selected from the group consisting of halo, C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_4alkoxy, C_3-C_6cycloalkyl, and nitro; or at least two alkyl substitutions of each of the L1 and L2 alkyl moietis can join together to each form a C3-C6cycloalkyl ring;;

or L_1 is absent;

and wherein the L_1 and L_2 heteroaryl and heterocycle moiety are each independently and separately optionally substituted with at least one substituent selected from C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, wherein the alkyl, alkenyl and

alkynyl groups are independently and separately optionally substituted with at least one substituent selected from hydroxyl, cyano, C_3-C_6 cycloalkyl, -NR^aR^b, C_1-C_4alkoxy, morpholine, and phenyl;

or halo, cyano, nitro, -NR^aR^b, oxo, hydroxyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, saturated or partially saturated C_3-C_6cycloalkyl optionally substituted with at least one substituent selected from C_1-C_3alkyl, amino, cyano, halo, -OH, and C_1-C_3alkoxy;

or phenyl optionally substituted with at least one substituent selected from halo, cyano, C_1-C_4alkyl, and C_1-C_4alkoxy;

or a saturated or partially saturated 4- to 6-membered heterocycle ring containing at least one heteroatom selected from N, O, and S and further optionally substituted with C_1-C_4alkyl;

or a 5- to 6-membered heteroaryl ring containing at least one heteroatom selected from N, O, and S and further optionally substituted with at least one substituent selected from halo, cyano, C_1-C_4alkyl, C_1-C_4haloalkyl and C_1-C_4alkoxy;

or -C(O)R, -COR, -C(O)OR, -$CS(O)_pR^a$, -$C(O)NR^aR^b$, -SR, -C(O)X, -OX, -$S(O)_pR$, -$S(O)_pX$, -$CNR^aC(O)R$, $CNR^aC(O)OR$, -CNR^aR^b, -$CNH_2(N)OH$, -$NR^aC(O)R$, -$NR^aC(O)OR$, -$NR^aS(O)_pR$, -$NR^aC(O)NR^aR^b$, -OR^e -$OR^eNR^aC(O)OR^e$, -$OR^eC(O)OH$;

R is C_1-C_6alkyl, amino, C_1-C_6haloalkyl, phenyl optionally substituted with at least one substituent selected from C_1-C_3alkoxy, cyano, halo, C_1-C_3alkyl, and C_1-C_3haloalkyl;

R^1, R^2, R^3, and R^4 are each separately and independently H and C_1-C_6alkyl;

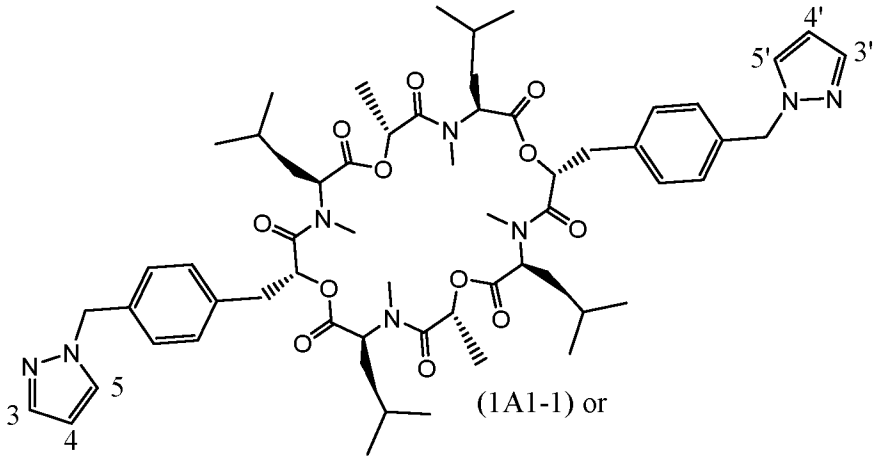
R^a and R^b are each separately H, C_1-C_6alkyl, C_1-C_3haloalkyl, C_3-C_6cycloalkyl, and phenyl optionally substituted with halo, amino, and C_1-C_3haloalkyl;

R^e is C_1-C_6alkyl optionally substituted with halo, amino, C_3-C_6cycloalky,and C_1-C_4alkoxy;

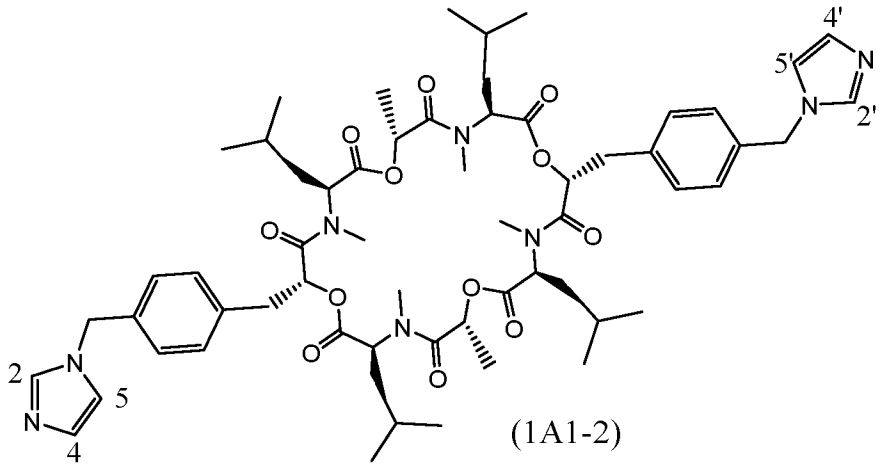
X is an N-linked 4- to 6-membered saturated or partially saturated heterocyclic ring optionally containing at least one additional heteroatom selected from N, O, and S; or X is a 5- to 6-membered heteroaryl ring containing at least one heteroatom selected from N, O, and S; or X is phenyl optionally substituted with at least one substituent selected from C_1-C_4haloalkyl, halo, amino, cyano, C_1-C_4alkyl, and C_1-C_4alkoxy; or X is a saturated or partially saturated C_3-C_6 cycloalkyl ring; and

p is the integer 0, 1, or 2, stereoisomers thereof, and veterinary acceptable salts thereof.

2. A compound of Formula (1) of Claim 1 that is a compound of Formula (1A1-1) or Formula (1A1-2)



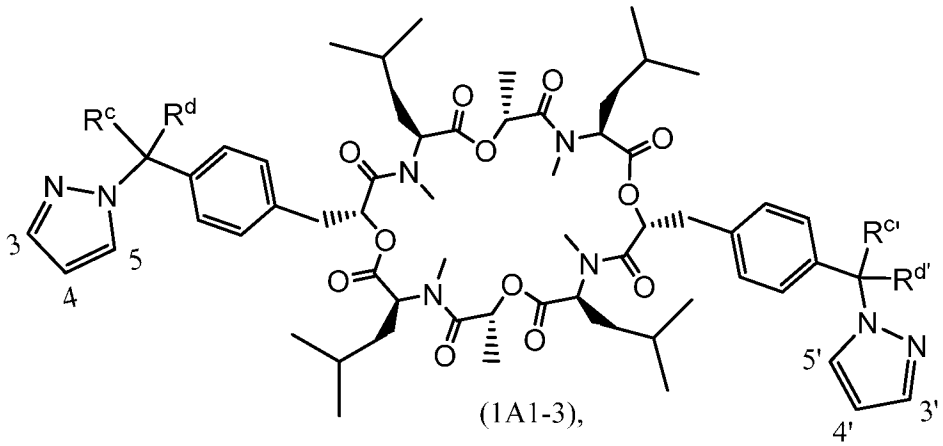
(1A1-1) or



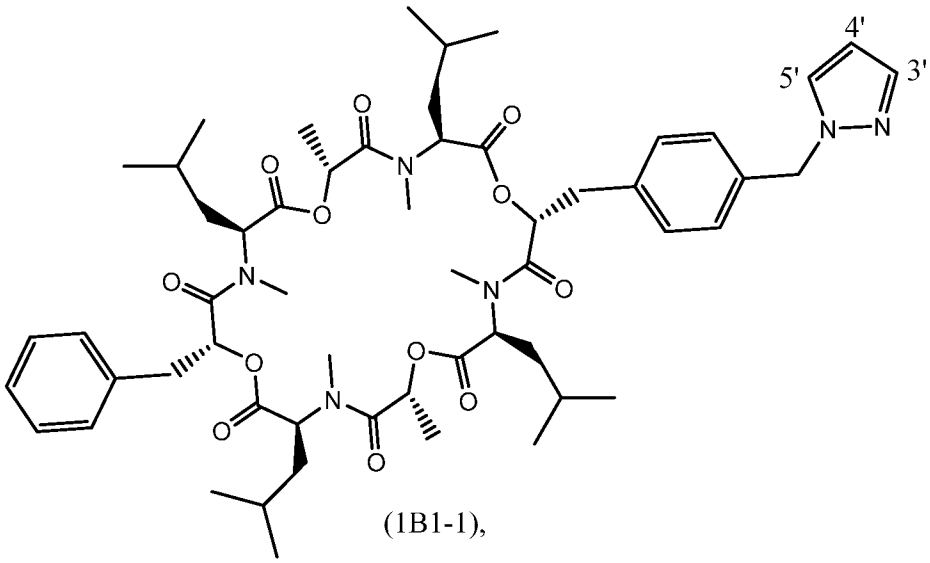
(1A1-2)

stereoisomers thereof, and veterinary acceptable salts thereof.

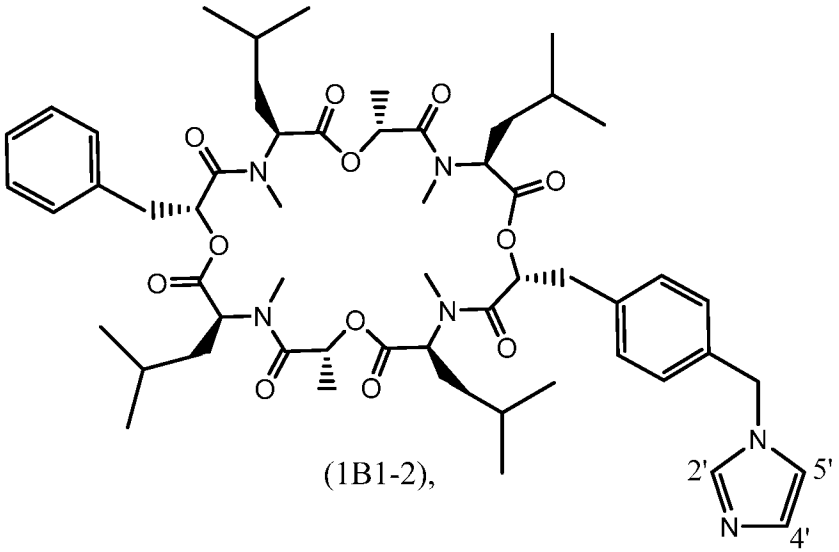
3. A compound of Formula (1) that is a compound of Formula (1A1-3), (1B1-1), Formula (1B1-2), Formula (1C1-1), Formula (1C1-2), Formula (1D1-1), (Formula (1E1), Formula (1F1), or Formula (1F2)



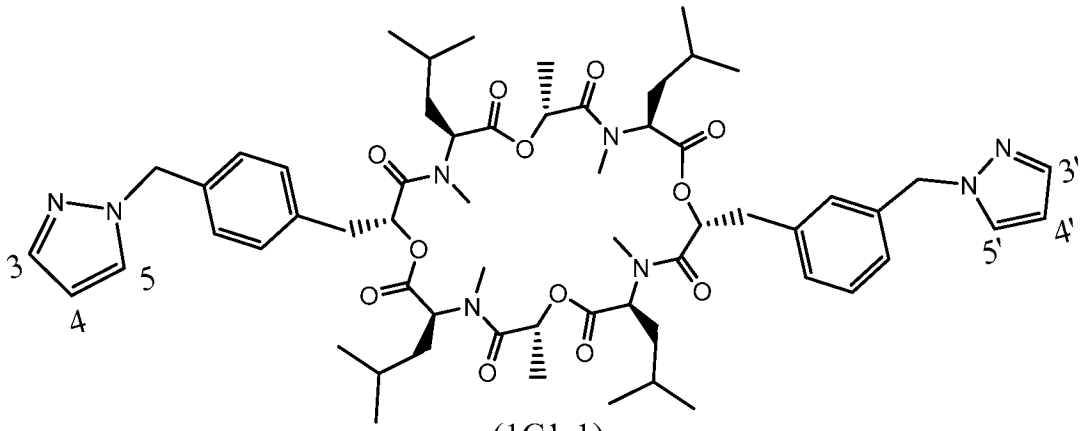
(1A1-3),



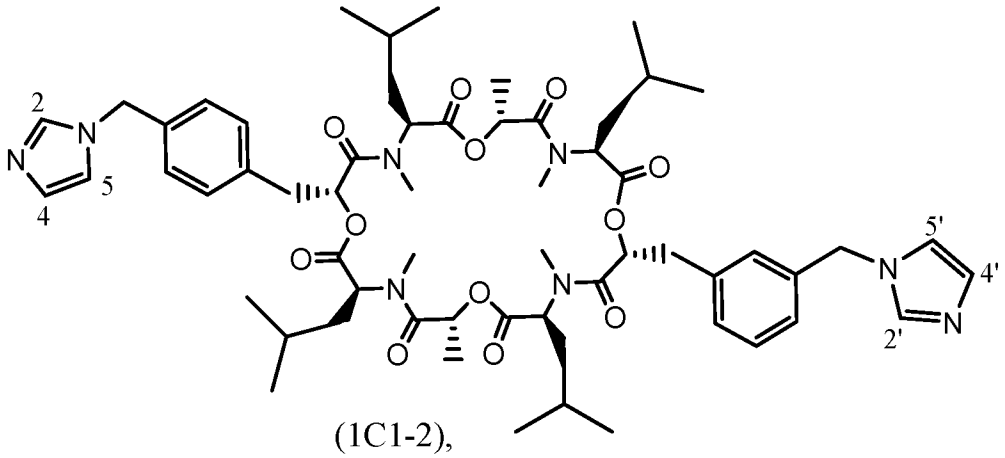
(1B1-1),



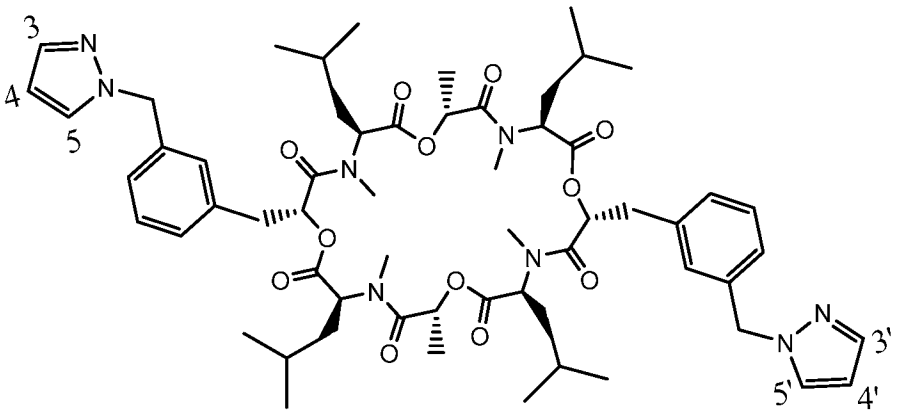
(1B1-2),



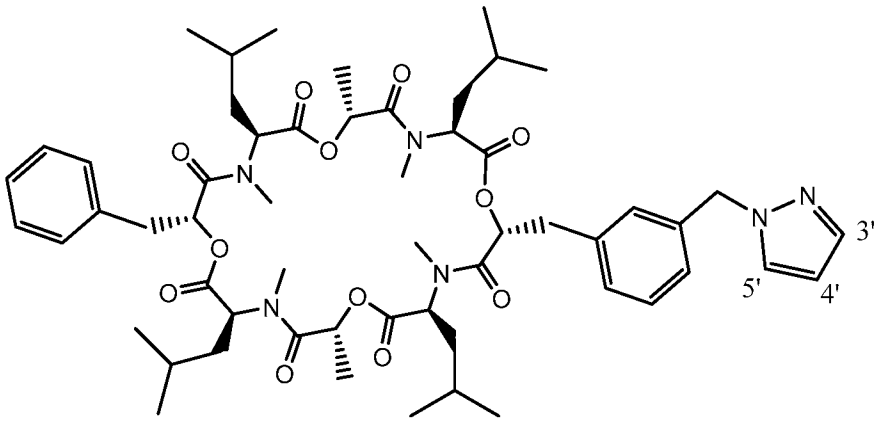
(1C1-1),



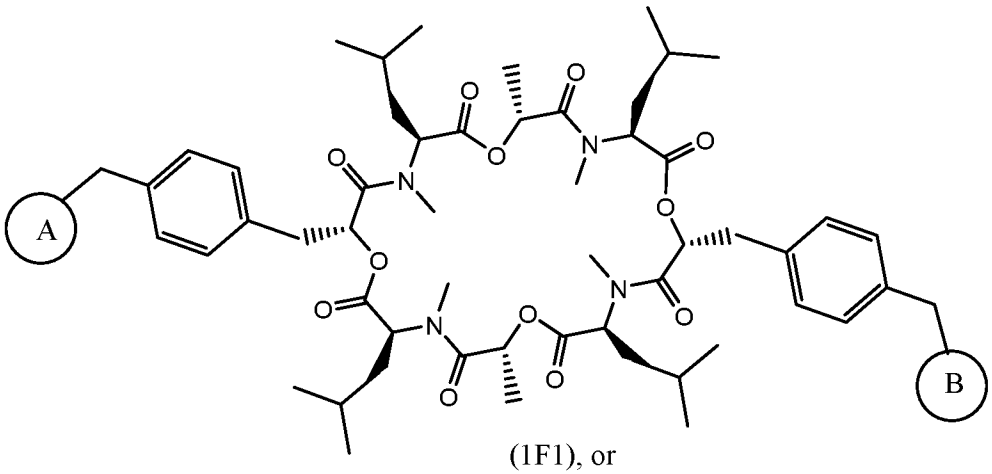
(1C1-2),



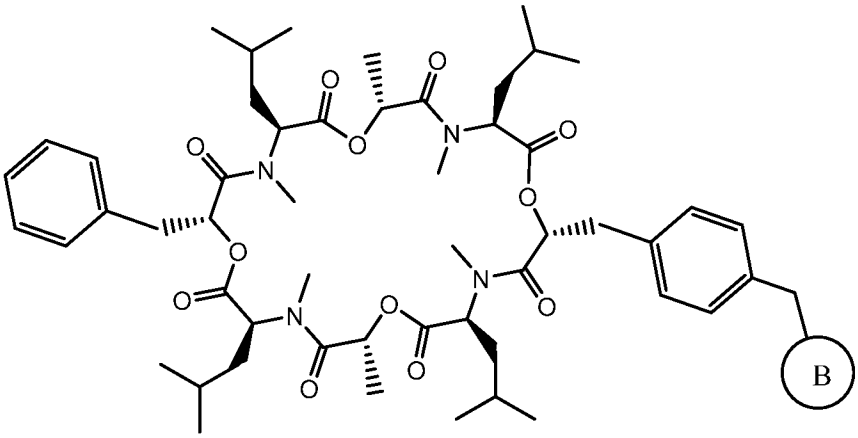
(1D1-1),



(1E1),



(1F1), or



(1F2)

stereoisomers thereof, and veterinary acceptable salts thereof.

4. A compound of Claim 2 that is a Formula (1A1-1) compound, stereoisomers thereof, and veterinary acceptable salts thereof.

5. A compound of Claim 4 that is a Formula (1A1-1) compound described in Table 1b, stereoisomers thereof, and veterinary acceptable salts thereof.

6. A compound of Claim 5 wherein each pyrazole is independently and separately optionally substituted with at least one substituent selected from C_1-C_6alkyl, halo, cyano, C_1-C_6haloalkyl, C_3-C_6cycloalkyl optionally substituted with at least one substituent selected from fluoro, chloro, methyl, and methoxy; C_1-C_6alkoxy, phenyl optionanlly substituted with at least one substituent selected from halo and methoxy; -C_1-cyclopropyl, and C_2-C_6alkynl optionally substituted with cyclopropyl or phenyl.

7. A copound of Claim 5 that is a compound selected from:
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis({4-[(3,5-dicyclopropyl-1H-pyrazol-1-yl)methyl]phenyl}methyl)-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[(4-{[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]methyl}phenyl)methyl]-4,10,12,16,22,24-hexamethyl-3,9,15,21-tetrakis(2-methylpropyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-chloro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-iodo-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-chloro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-

1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((3-chloro-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopropyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((4-(3-methylbut-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(cyclopropylethynyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-(but-1-yn-1-yl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-isopropyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(tert-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclobutyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;

(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-(4-methoxyphenyl)-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((3-isopropoxy-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(4-chlorophenyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-cyclopentyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-(2-(4-ethoxy-1H-pyrazol-1-yl)propan-2-yl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((4-isobutoxy-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-ethoxy-3-phenyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6-(4-((5-ethyl-3-methyl-1H-pyrazol-1-yl)methyl)benzyl)-18-(4-((3-ethyl-5-methyl-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(cyclopropylmethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-6,18-bis(4-((5-isobutyl-1H-pyrazol-1-yl)methyl)benzyl)-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;

(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(sec-butyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(1-fluorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(2,2-difluorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(1-chlorocyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(1-methylcyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
(3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis(4-((5-(2-methylcyclopropyl)-1H-pyrazol-1-yl)methyl)benzyl)-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone;
((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis[[4-[(4-ethoxypyrazol-1-yl)methyl]phenyl]methyl]-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone);
((3S,6R,9S,12R,15S,18R,21S,24R)-3,9,15,21-tetraisobutyl-4,6,10,16,18,22-hexamethyl-12,24-bis[[4-(pyrazol-1-ylmethyl)phenyl]methyl]-1,7,13,19-tetraoxa-4,10,16,22-tetrazacyclotetracosane-2,5,8,11,14,17,20,23-octaone); and
((3S,6R,9S,12R,15S,18R,21S,24R)-6,18-bis(4-((5-(difluoromethyl)-1H-pyrazol-1-yl)methyl)benzyl)-3,9,15,21-tetraisobutyl-4,10,12,16,22,24-hexamethyl-1,7,13,19-tetraoxa-4,10,16,22-tetraazacyclotetracosan-2,5,8,11,14,17,20,23-octaone);
stereoisomers thereof, and veterinary acceptable salts thereof.

8. A composition comprising a compound of any one of the preceeding Claims, and further comprising a veterinary acceptable excipient.

9. The composition of Claim 8, further comprising at least one additional antiparasitic agent.

10. A method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1-1) or (1A1-2) compound of Claim 2; or a method of treating a parasitic infection in an animal in need thereof by administering an effective amount of a Formula (1A1-3), (1B1-1), Formula (1B1-2), Formula (1C1-1), Formula (1C1-2), Formula (1D1-1), (Formula (1E1), Formula (1F1), or Formula (1F2) compound of Claim 3.

11. The method of Claim 10 wherein the effective amount of the compound is administered to the animal in need thereof by oral, injectable, or topical administration.

12. The method of Claim 10 wherein the parasitic infection is an endoparasitic infection.

13. The method of Claim 12 wherein the endoparasitici infection is caused by a filarial parasite.

14. The method of Claim 13 wherein the filarial parasite is a Dirofiliaria parasite and the animal is a companion animal.

15. Use of a compound of Formula (1) of Claim 1; or a Formula (1A1-1) or Formula (1A1-2) of Claim 2; or a Formula (1A1-1) of Claim 4, Claim 5, Claim 6, or Claim 7; or a Formula (1A1-3), (1B1-1), (1B1-2), (1C1-1), (1C1-2), (1D1-1), (1E1), 1F1, or 1F2 of Claim 3; to prepare a medicament for treating an endoparasitic infection in an animal in need thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/062749

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/14 A61K38/15 C07D413/10 C07K11/02 A61P33/00
C07D417/14 C07D471/04 C07D487/04 C07D491/052 C07D498/04
C07D513/04 A01N43/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K C07K A61P A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2016/187534 A1 (MERIAL INC [US]) 24 November 2016 (2016-11-24)	1,3,8-15
A	compounds in Tables 1, 15, 19, 35 and 36; Biological Methods A-D on pages 367-371; claims 1,29-33	2,4-7

Y	WO 98/55469 A1 (BAYER AG [DE]; DYKER HUBERT [DE]; SCHERKENBECK JUERGEN [DE]; HARDER AC) 10 December 1998 (1998-12-10)	1,3,8-15
A	compounds on page 61; page 33, lines 29-32; claims 1,8-10	2,4-7

X	WO 99/66794 A1 (BAYER AG [DE]; JESCHKE PETER [DE]; TURBERG ANDREAS [DE]; MENCKE NORBER) 29 December 1999 (1999-12-29) compounds of Examples 1-18; page 14, paragraph 2; claims 1,2; examples A-D	1,3,8-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2019	18/02/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Guspanová, Jana

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/062749

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 2016187534	A1	24-11-2016	AR	104714	A1	09-08-2017
			AU	2016264635	A1	14-12-2017
			BR	112017024773	A2	06-11-2018
			CA	2986478	A1	24-11-2016
			CL	2017002936	A1	16-03-2018
			CN	107835818	A	23-03-2018
			CO	2017011738	A2	09-02-2018
			EP	3298027	A1	28-03-2018
			JP	2018516904	A	28-06-2018
			KR	20180002886	A	08-01-2018
			PH	12017502106	A1	28-05-2018
			TW	201706287	A	16-02-2017
			US	2017022253	A1	26-01-2017
			US	2018362589	A1	20-12-2018
			UY	36683	A	30-12-2016
			WO	2016187534	A1	24-11-2016
WO 9855469	A1	10-12-1998	AU	735424	B2	05-07-2001
			BR	9810412	A	22-08-2000
			CA	2292698	A1	10-12-1998
			CN	1259129	A	05-07-2000
			EP	0986549	A1	22-03-2000
			HK	1028605	A1	02-08-2002
			JP	2002502398	A	22-01-2002
			NZ	501478	A	25-05-2001
			US	6355615	B1	12-03-2002
			WO	9855469	A1	10-12-1998
WO 9966794	A1	29-12-1999	AT	229269	T	15-12-2002
			AU	751711	B2	22-08-2002
			BR	9912199	A	10-04-2001
			CA	2336129	A1	29-12-1999
			CN	1306394	A	01-08-2001
			DE	19828043	A1	30-12-1999
			DK	1089625	T3	24-03-2003
			EP	1089625	A1	11-04-2001
			ES	2186371	T3	01-05-2003
			HU	0102808	A2	28-11-2001
			JP	4404484	B2	27-01-2010
			JP	2002518415	A	25-06-2002
			NZ	509105	A	20-12-2002
			PT	1089625	E	30-04-2003
			US	6630569	B1	07-10-2003
			WO	9966794	A1	29-12-1999